# HISTOPATHOLOGICAL ANALYSIS AND Ki- 67 EXPRESSION IN VARIOUS CENTRAL NERVOUS SYSTEM TUMORS

**DISSERTATION**

**SUBMITTED FOR M.D (PATHOLOGY)**

**BRANCH III**

**APRIL – 2013**


**THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY**
**CHENNAI – TAMILNADU**

# CERTIFICATE

This is to certify that this dissertation entitled **"HISTOPATHOLOGICAL ANALYSIS AND Ki 67 EXPRESSION IN VARIOUS CENTRAL NERVOUS SYSTEM TUMORS"** is the bonafide record of the research work done by Dr. V.Martina, submitted as partial fulfilment for the requirements of M.D Degree Examination( Pathology) to be held in April 2013, in the Department of Pathology, Thanjavur Medical College, Thanjavur.

I also certify that this dissertation is an independant work done by the candidate

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# CERTIFICATE

This is to certify that this dissertation entitled **"HISTOPATHOLOGICAL ANALYSIS AND Ki-67 EXPRESSION IN VARIOUS CENTRAL NERVOUS SYSTEM TUMORS"** is the original and bonafide work done by **Dr.V.Martina** under my guidance and supervision at Thanjavur Medical College , Thanjavur, during the tenure of her course in M.D. Pathology from May 2010 to April 2013 held under the regulation of the Tamilnadu Dr.M.G.R. Medical University, Guindy, Chennai- 600032.

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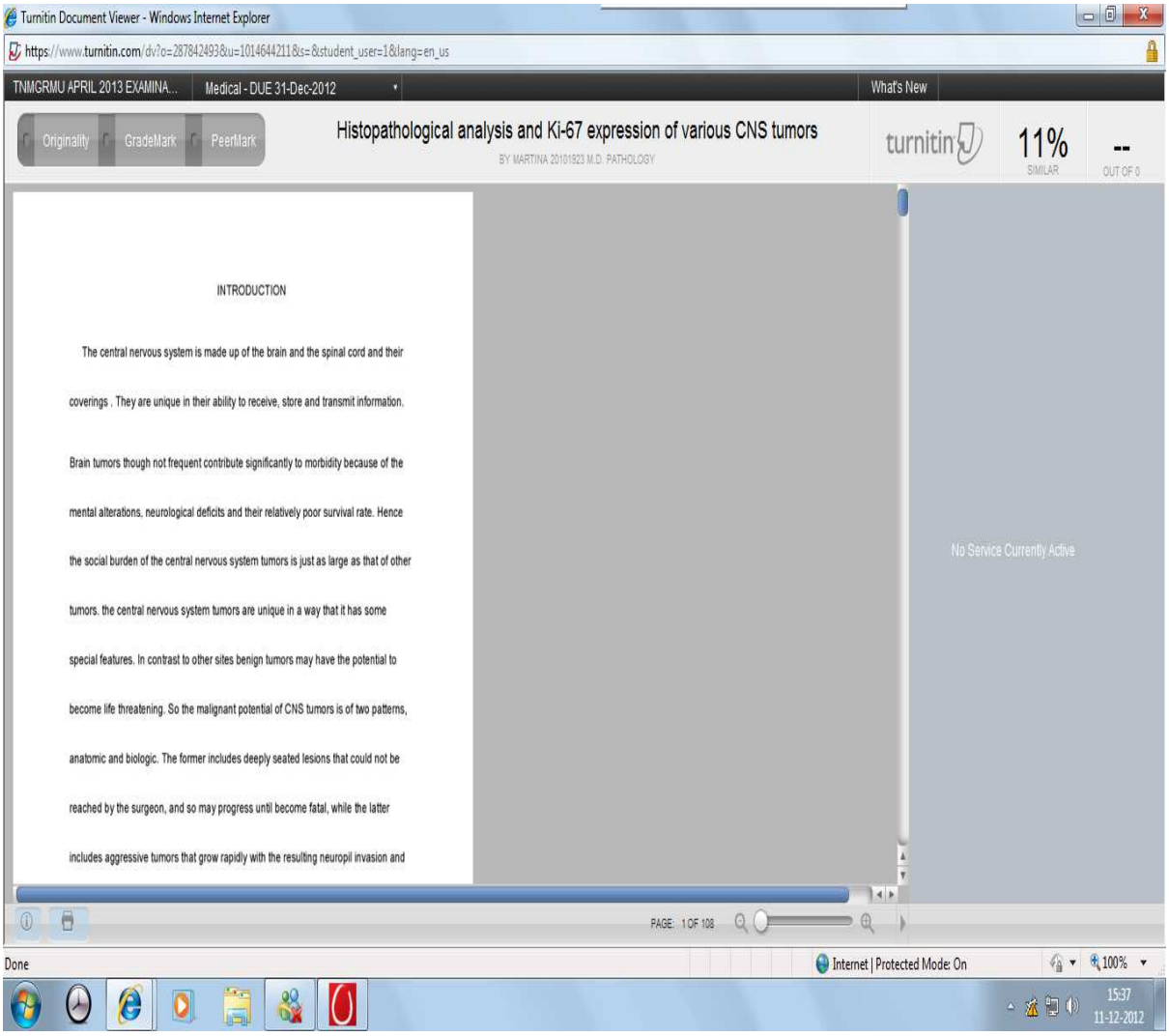
# ANTIPLAGIARISM ORIGINALITY REPORT



# ACKNOWLEDGMENT

I wish to express my gratitude to **Professor Dr. N. Arumugam, M.D.,** Head of the Department of Pathology, Thanjavur Medical College, for his valuable guidance, constant encouragement and words of advice, right from the selection of the topic till the completion of the dissertation.

I am immensely thankful to **Dr. A.Vasahar, M.D., Associate Professor** for being my guide and encouraging me. His criticisms and corrections at each stage of the study made me correct my mistakes and improve the quality of the study.

I am also extremely grateful to **Professor Dr.M.Saraswathi, M.D.,DGO.,** and **Professor Dr.AL.Santhi M.D.,DGO.,** who offered me many valid suggestions and encouraged me often during the period of my study. I express my sincere gratitude to **Dr. M.Senthil Kumar M.D.,** and **Dr. K.G. Padmanaban M.D., Associate Professors,** for their motivating words.

I gratefully acknowledge all the help and constant support from **Dr. S.Jenita Christiana Ranjana M.D.,** and **Dr.V. Sindhu M.D.,** A**ssistant Professors**. By sharing their knowledge and experiences, they moulded my work and gave this dissertation a proper form.

I would like to extend my sincere and heartfelt gratitude to all the laboratory technicians and all the staffs of the department for their generous and timely help without which this study would not be completed. I sincerely thank my fellow postgraduates for their inspiration and co-operation throughout the study period.

I thank the **DEAN, Thanjavur Medical College,** Thanjavur, for allowing me to pursue this study work in this institution.

Above all I thank the Almighty for giving me the wisdom and knowledge to complete this dissertation.

# CONTENTS

# *INTRODUCTION*

# INTRODUCTION

The central nervous system is made up of the brain and the spinal cord and their coverings . They are unique in their ability to receive, store and transmit information.

Brain tumors though not frequent contribute significantly to morbidity because of the mental alterations, neurological deficits and their relatively poor survival rate. Hence the social burden of the central nervous system tumors is just as large as that of other tumors. The central nervous system tumors are unique in a way that it has some special features. In contrast to other sites benign tumors may have the potential to become life threatening. So the malignant potential of CNS tumors is of two patterns, anatomic and biologic. The former includes deeply seated lesions that could not be reached by the surgeon, and so may progress until become fatal, while the latter includes aggressive tumors that grow rapidly with the resulting neuropil invasion and destruction. Nevertheless CNS cancers do not fit exactly the general definition of malignancy as they rarely spread outside their primary location, despite the fact that some tumors tend to seed the neuraxis via CSF[44].

Space occupying primary neoplasms of the CNS and its covering account for about 9% of all primary neoplasms of the human body and metastatic tumors constitute about 5% [75]. Among the intracranial space occupying tumors those of

the central neurogenic origin claim priority in number and complexity. These are the tumors derived from parenchymatous neuroepithelial elements of the CNS excluding microglia; and they are widely credited to account for 40-50% of all intracranial space occupying tumors[62]

Systematic study of tumors of the CNS began when Bailey and Cushing started their studies in the early 1920's. Over the past three decades, many reports suggested that both incidence and pattern of intracranial neoplasia are subject to considerable geographic and racial variations. Population based cancer registries are established for a better understanding of the epidemiology . knowledge of the regional peculiarities of these lesions may therefore help in identification of possible risk factors. Delay in reporting are a reality and a known issue influencing registry completeness for achieving data quality goals. Ultimately it will affect the magnitude of rate calculation leading on to cancer rate underestimation, that will hinder the planning measures for updated facility treatment centers. Hence it is essential that quality control editing of the data with incorporation of updates to the cancer registration has to be refined every year.

Primary brain tumors continue to be among the top ten causes of cancer related deaths in the world. As per the CBTRUS( Central Brain Tumor Registry of the United States), the annual incidence of the tumors of the CNS is 3.9 per 100,000 persons for intracranial tumors. Global differences in rates tend to

correspond to the level of economic development, with the highest rates in North America, Australia, and Western Europe and the lowest rates in Asia, South and central America. Regional differences in incidence rates of CNS tumors were also noted in India. According to the data obtained from various cancer registries in India the age specific ,world adjusted incidence rate accounts to be 5.1 per 100,000 persons. The highest incidence of brain tumors was reported from Sikkim and lowest in Mizoram state.[75]

Risk factors causing brain tumors remain uncertain. Racial differences, exposure to radiation, chemical exposure in working in the rubber, petrochemical or metal industries and family history of brain cancer are postulated to increase the risk of brain tumors. Excessive use of mobile phones resulting in exposure to electromagnetic waves has triggered a great inquisition among researchers to label it as a cause for brain tumors, but its etiopathogenesis is still not proven. So epidemiological studies of brain tumors in depth is necessary to understand the etiology of risk factors.

An estimated 2400 children between the ages of 0-19 years are diagnosed with invasive primary CNS tumors in the United States each year[109]. The incidence of CNS tumors in children < 20 years is 4.58 per 100,000 person years. (CBTRUS report 2009). Brain tumors are second only in frequency to acute lymphoblastic leukemia in children. Pilocytic astrocytomas, malignant glioma and medulloblastoma are the commonest tumors. The incidence of CNS

tumors in children was found to have increased in the recent years. This incidence has been mainly attributed to the introduction of Magnetic Resonance Imaging (MRI) in the 1980s that improved the detection of low grade tumors previously unidentifiable by other less optimal imaging modalities.

A comparison using international studies of primary intracranial tumors results in an average male to female ratio of 1.4:1 across geographical areas. However sex ratios varies considerably by histological types. Gliomas are higher in males and females show a predominance with meningiomas.[1]

The CNS tumors have always been a cause of concern to the pathologist due to the wide variety in their appearances. Diagnosing a CNS tumor posses a significant challenge but the gold standard used for the definitive diagnosis of CNS tumors is the microscopic examination of the tumor

The WHO 2007 classification is the latest updated system that has been edited by two neuropathologists ( Dr. Louis and Dr. Weistler) and two molecular pathologists ( Dr.Ohgaki and Dr.Cavenee), reflecting the gradual shift in modern pathology. About 86 major types of CNS tumors and their variants have been listed.[52]

Grading is fundamental for optimal prognostication and deciding on the choice of therapy. Histological grading of CNS tumors can be challenging despite criteria given by WHO more often due to limited tumor material

provided. The number of mitosis is of paramount importance but can be hard to identify in the haematoxylin and eosin stained sections. Since proliferative activity is  a reliable method to assess tumor biology estimation of proliferative activity has gained much enthusiasm and there has been continuous research to employ biological markers such as Ki -67 as an adjunct to conventional morphological variables.

The diagnostic tools in the investigation of brain tumors are expanding greatly with advances in imaging studies. These modalities are complementary to the diagnosis and are not confirmatory. Immunohistochemistry is an essential clinical research tool in medical science in this era. It helps in making specific confirmatory diagnosis by detecting lesion specific markers. It also helps in predicting the final outcome of neoplastic lesion by detecting various prognostic markers

Ki -67 is a novel non histone nuclear protein that is expressed in the active phases of the cell cycle and thus labelling with the monoclonal antibody against this antigen readily identifies cells that are actively proliferating. Ki-67 labelling correlated well and yielded credible results in our study. However this marker should not be used alone but in combination with established histopathological criteria of malignancy.

# *AIM OF THE STUDY*

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## AIM OF THE STUDY

1. To study the incidence of various CNS neoplasms reported in the department of Pathology, at Thanjavur Medical college.
2. To evaluate the anatomical distribution of CNS neoplasms.
3. To determine the age and sex wise distribution of CNS neoplasms of various grades.
4. To histologically grade CNS neoplasms according to WHO 2007 criteria.
5. To evaluate the occurrence of various childhood brain tumors
6. To evaluate the expression of Ki - 67 in different CNS neoplasms.

# *MATERIALS AND METHOD*

## MATERIALS AND METHODS

This study was carried out in the department of Pathology from January 2010 to May 2012 (29 months). All specimens sent with the clinical diagnosis of central nervous system tumors were studied and only histologically diagnosed CNS neoplasms were included. All the tumors were graded according to the WHO criteria.

**Exclusion criteria:**

1. Reactive lesions
2. CNS infections
3. Non neoplastic cystic lesions

The specimens were mostly biopsies received as an aggregate ranging from 0.5 cc to 5 cc. There was one specimen of meningioma which was received as a well circumscribed mass measuring 5 x 5 cms .(fig 1) A detailed history with particular attention to clinical symptoms and signs were noted. Site of the tumors were recorded and correlated with the computed tomography findings.

All the specimens were fixed in 10% neutral formalin and were subjected to histopathological examination. Sections of 3-5 micron thickness were made and routine staining with haematoxylin and eosin was done.( Annexure - III)

Reticulin stain was applied to one case of Gliosarcoma for confirmation of the sarcomatous component ( Annexure- IV) along with GFAP for highlighting the glial elements for the same case.

Immunohistochemistry was done with Ki 67 antibody for selected cases that included different tumors of various grades. Immunohistochemistry was done based on the peroxidise method with a standard HRP kit. (Annexure- V).

# *REVIEW OF LITERATURE*

**REVIEW OF LITERATURE**

## ANATOMY

The CNS consists of the brain and the spinal cord covered by the meninges. All parts of the CNS are made up of the gray matter containing mainly the neuronal cell bodies and the white matter that has the axons. The supporting cells are the neuroglia that comprise four principle type of glial cells – astrocytes, oligodendrocytes, microglia and ependymal cells. The astrocytes are highly branched cells that pack the interstices between the neurones. They provide mechanical support and mediate exchange of metabolites and form blood brain barrier. It also has an important role in the repair of CNS tissue after injury. Oligodendrocytes are CNS equivalents of the Schwann cells of the PNS and for myelin. The microglia are CNS representatives of the monocyte-macrophage system. Ependymal cells form the specialised epithelium which lines the ventricles and spinal canal and secrete the CSF[120]

## EPIDEMIOLOGY OF BRAIN TUMORS:

According to the data of the CBTRUS ( Central Brain Tumor Registry of the United States) [12] the overall rate of occurrence of CNS tumors is about 19.34 per 100,000 person years. N.Manoharan et al[75] showed that the CNS tumors were more common in the male population (65%) than in the females in India.

**ETIOLOGY OF BRAIN TUMORS**

Exposure to ionising radiation is the only well documented environmental risk factor for the development of gliomas. The mutations in the genes causing brain tumors are usually the tumor suppressor genes and the protooncogenes[2]. A number of hereditary syndromes as shown in the table are asociated with brain tumors. Astrocytomas have EGFR amplifications and PDGFR amplifications sometimes associated with LOH 10q(PTEN) and LOH at 9p( INK 4a). Oligodendrogliomas have del 1p and 19q. In meningiomas portions of chromosome 22 q are lost. The results of neither the case-control studies nor the meta-analysis conducted by the INTERPHONE study, coordinated by the International Agency for Research on Cancer (IARC) provide consistent support for an association between mobile phone use and brain tumours.[92]

Common genetic syndromes and associated tumors[109]

| SYNDROME | GENE | CHROMOSOME | TUMORS |
|---|---|---|---|
| Neurofibromatosis Type I | NF-1 | 17q11 | Optic gliomas,<br>Asrocytomas<br>Neurofibromas |
| Neurofibromatosis Type II | NF-2 | 22q12 | Vestibular schwannomas<br>Meningiomas<br>Spinal cord ependymomas |
| Von Hippel Lindau | VHL | 3p25 | Cerebellar hemangioblastomas |
| Tuberous sclerosis | TSC1 and TSC2 | 9q34 and 16p13 | Subependymal giant cell astrocytoma |
| Turcot | APC, MLH1,PMS-2 | 5q21,3p21,7p21 | Medulloblatoma<br>Glioblastoma multiforme |
| Gorlin | PTCH | 9q31 | Medulloblastoma |
| Li- Fraumeni | P53 | 17P13 | Astrocytoma<br>PNET |

## CLASSIFICATION OF CNS TUMORS

The first comprehensive classification of CNS tumors formulated by Percival Bailey and Harvey Cushing in 1926 was based on the embryology and histology of the neoplastic cells[117]. Russel and Rubinstein continued to modify and update previous systems. The WHO classification 2007 edited by Dr. Oghagi and Dr.Louis is currently in use widely.[51] WHO classifies CNS tumors into tumors of the neuroepithelial tissue that include astrocytomas, oligodendrogliomas, ependymomas and medulloblastomas, the tumors of the meninges, tumors of the cranial and paraspinal nerves , lymphomas, and hematopoietic neoplasms, germ cell tumors, tumors of the sellar region and metastatic tumors.

## GRADING SYSTEMS

Grading of the CNS tumors are done to represent the nature of the tumor and therefore predict the patient survival. This is particularly useful for astrocytomas that have different treatment protocols for various grades. Previously, St. Anne Mayo system was used based on the four criteria of atypia of the nucleus, mitosis, microvascular proliferation and necrosis. The WHO also considers the above criteria but designates different terminologies for the tumors. Starting with the most benign as grade I, numerical grades II, III,IV represent increasing malignancy. Numerical grades assigned by the WHO are used in this dissertation. There are definitive criteria for grading most of the

CNS neoplasms according to the WHO, in particular for astrocytomas, meningiomas and oligodendrogliomas and epedymomas.

**GLIOMAS**

Glioma is a term that embraces astrocytomas, ependymomas and oligodendrogliomas. Astrocytomas are heterogenous neoplasms with various subtypes[116]

**ASTROCYTOMA:**WHO grading and criteria for astrocytomas.

| **WHO grade** | **WHO designation** | **Histological criteria** |
|---|---|---|
| I | Pilocytic astrocytoma | Circumscribed, biphasic: bipolar piloid cells;microcysts, Rosental fiblres ,rare mitotic figures,vascular proliferation or focal necrosis |
| II | Diffuse astrocytoma | Moderate hypercellularity of monotonous cells; mild nuclear atypia; no or minimal mitotic activity |
| III | Anaplastic astrocytoma | Increased cellularity and diffuse infiltration ; increased nuclear atypia; increased mitotic activity increased |
| IV | Glioblastoma multiforme | Vascular proliferation or necrosis; crowded anaplastic cells; marked nuclear atypia; brisk mitotic activity. |

**PILOCYTIC ASTROCYTOMA:**

Pilocytic Astrocytoma is a grade I tumor that accounts for 2% of all CNS tumors they are more common in children and accounts for 85% of cerebellar astrocytomas

**Gross**: cystic and well demarcated. May appear spongy because of microcysts

**Microscopy** : It has a biphasic dense and loose appearance. Piloid astrocytes with long hair like processes are characteristic. Though not diagnostic Rosenthal fibres and PAS positive eosinophilic granular bodies are seen in most cases. It has a good prognosis. Rosenthal fibres are highly eosinophilic, hyaline structures. They are round, oval or beaded with slightly irregular margins resembling cracked glass, resulting from their formation within glial process. They contain ubiquinated alpha B – crystalline which can be identified by IHC. Eosinophilic granular bodies consist of droplets of protein sometimes found in

association with Rosentahl fibres. These protein droplets are bright pink and are PAS positive and can be stained with alpha 1- antichymotrypsin.

**PILOMYXOID ASTROCYTOMA:**

They are similar to pilocytic astrocytoma and are typically found in very young children . It has bipolar cells that clusters around blood vessels, but its parenchyma is more pilocytic than ependymomatous. It also characteristically

has a mucinous matrix. CSF spread and local recurrences are more common. PXA is considered a grade II tumor according to the WHO.

**DIFFUSE ASTROCYTOMA**: There are three distinct variants of astrocytoma

1. **Fribrillary astrocytoma**: They are most common tumors in the cerebral hemispheres. When occurs in the brain stem they are associated with poor prognosis[5]

   **Gross**: mass lesion in the gray or white matter with indistinct boundaries

   **Microscopy**: Hypercellular tumor, and has an infiltrating borders with hyperchromatic oval to spindle nucleus. Presence of mild to moderate atypia.

2. **Gemistocytic astrocytoma**: Gemistocytes are neoplatic astrocytes with a round hyperchromatic nucleus and a eccentrically placed hyaline pink cytoplasm packed with GFAP fibrils. Tihan et al[113] has said neoplastic gemistocytes should comprise approximately 20% of the neoplasm. They have a male predominance and occur exclusively in the supratentorial compartment. They are clinically aggressive tumors and progress to high grade astrocytomas. The differential diagnosis for gemistocytes are the minigemistocytes of oligodendroglioma, reactive astrocytes and gangliogliomas.

3. **Protoplasmic astrocytoma**: this tumor has overlapping features with pilomyxoid astrocytomas and oligoastrocytoma. They are composed of tumor cells with oval, hyperchromatic nucleus and thin wispy processes creating a cob web like growth pattern.

**ANAPLASTIC ASTROCYTOMA**:

The most common age group of occurrence is the fourth decade.

**Gross**: Solid tumor exhibiting friable gray granular tumor tissue merging with the surrounding brain marked enlargement of gyri and basal ganglia.

**Microscopy** : presence of increased cellular density. and increased mitosis. But absence of microvascular proliferation and necrosis is the characteristic of this grade of astrocytoma. Rule of thumb for evaluating cellular density is that

the average distance between a nucleus and its nearest cell should not be less than the average nuclear diameter according to Johan M Kros[46]

Average survival of patients with anaplastic astrocytoma is around 2 years. Rarely anaplastic astrocytomas are associated with hereditary colonic polyposis or neurofibromatosis.

**GLIOBLASTOMA MULTIFORME:**

It represents one quarter of all adult gliomas and constitutes about 15% of pediatric gliomas. They are most often centered in the white matter. Peak age of occurrence is in the fifth decade. A cerebellar glioblastoma is very rare in all age groups. A denovo GBM occur as a result of EGFR amplification. Secondary GBM occur as a result of progression from a low grade astrocytoma according to Taiichi Saito et al[112]

**Gross** : Poorly delineated mass, has a variegated appearance with areas of haemorrhage and necrosis. Multifocal occurrence is common. Blurred tumor-brain interface and gray- white matter junction commonly occurs.

**Microscopy:** Markedly cellular tumor composed of highly anaplastic cells with significant nuclear pleomorphism. Vascular proliferation, mitotic activity and necrosis with or without pseudo pallisading tumor cells are features.

**GLIOSARCOMA**:

It is a high grade glioma and a variant of GBM. According to Gilanis et al [34]It accounts for < 2% of all gliomas and 5 % of astrocytomas. They have both astrocytic and sarcomatous components. They represent a mesenchymal metaplasia in the glioma. The sarcomatous element is usually a fibrosarcoma or MFH. The sarcomatous element do not stain with GFAP but stain with reticulin stain.

Genetically the gliosarcomas are similar to primary GBM except that they have not been shown to have amplifications of EGFR.[92]

**GLIOMATOSIS CEREBRI**:

Diffuse growth pattern where neoplastic glia spread widely throughout the brain frequently involving more than two lobes and is frequently bilateral. Involvement of thalamus and basal ganglia is common. Bilateral tumors with thalamus and basal ganglia involvement is common according to Lopes MBS et al[58]

**SUBEPENDYMAL GIANT CELL ASTROCYTOMA (SEGA)**

It is a benign intraventricular tumor nearly exclusively occurring in the setting of tuberous sclerosis. Tuberous sclerosis is an autosomal dominant syndrome that causes hamartomatous neoplasms. It is associated with mutations in the TSC 1 and TSC 2 gene on chromosome 9 and 16 respectively. These tumor

suppressor genes produce protein hamartin and tuberin. It is typically located in the lateral or third ventricle. Mostly occurs in the children and young adults and accounts for less than 1% of the intracranial tumors.

**Gross**: Solid, well demarcated often calcified tumor. 'Candle guttering' represent small wax dripping like appearance within the ventricle.

**Microscopy**: Epithelioid, gemistocyte like or spindle cells arranged in sweeping fascisle, dysmorphic cells with neuron like nucleolus. Perivascular pseudorosettes are common.

**PLEOMORPHIC XANTHOASTROCYTOMA**:

PXA is a specialised variant of astrocytoma with predilection for the superficial cortex occurs mostly in children.

**Gross**: Well demarcated, solid and rubbery consistency. Cystic components and calcifications are common.

**Microscopy: T**hey are characterised by foci of pleomorphic astrocytes and spindled mesenchymal like cells arranged in fascicles or a storiform pattern. Multinucleated cells are common. Lipidized astrocytes (xanthoastrocytes) are seen in one fourth of cases. Rosenthal fibres and eosinophilic granular bodies

may be seen occasionally. Astrocytes are confirmed by the strong GFAP positivity. These cells are surrounded by reticulin fibres.

**ASTROBLASTOMA:**

It is a rare cerebral glioma of unknown histiogenesis. It occurs in children.

**Gross:** solid and relatively well demarcated, may be cystic or necrotic.

**Microscopy**: It has mixed astrocytoma and ependymoma like features. Grow in a circumscribed fashion and have perivascular pseudorosette. The perivascular

GFAP rich cytoplasmic processes are broad and stout than that in ependymomas and remain thick throughout the entire thickness from cell body to adventitia of the vessel. There is extensive vascular hyalinisation. Astrocytomas may express focal GFAP, they do not stain with PTAH. This may be due to the expression of a non fibrillar form of GFAP molecule.

**OLIGODENDROGLIOMA:**

They represent the second major category of diffuse glioma with an incidence of 5 -15%. With an annual incidence of 0.5 per 100000 person years. (CBTRUS)[14] They typically affect middle aged adults( 40- 45 years). Common in the frontal lobe. It is more common in males according Mork et al[73] . 50-90% cases show co-deletion of 1p and 19 q according to the study of Louis et al[59]

**Gross:** borders are ill defined with blurring of gray- white matter interface, calcification, cystic degeneration and hemorrhage are present. WHO criteria for grading of oligodendrogliomas is shown below.

| Grade | Nomenclature | Histological features |
|---|---|---|
| II | Oligodendroglioma | Moderate cellularity; homogeneously round nuclei, “fried egg” halo (paraffin sections); fine capillary network; mineralisation (microcalcifications) |
| III | Anaplastic oligodendroglioma | Increased cellularity; high mitotic rate; marked cytologic atypia; microvascular proliferation |

**Microscopy**: Tumor is composed uniformly round to oval nuclei with bland chromatin and often small nucleoli and. Clear perinuclear halos impart a ‘fried

egg' appearance and occur as a result of formalin fixation artefact. Rich branching capillary network resembling 'chicken wire' are seen. Anaplastic oligodendrogliomas have frequent mitosis, endothelial hyperplasia, increased pleomorphism and epithelioid cytology.

**OLIGOASTROCYTOMA:**

**Gross**: well defined soft masses of greyish colour. Mucoid degeneration, calcification and cystic change are often present.

**Microscopy**: Tumor is composed of mixture of two distinct neoplastic cell types with microcalcification and microcystic degeneration. It may be divided into biphasic of intermingled variants. It is important to differentiate between oligoastrocytomas and pure astrocytomas as oligoastrocytomas respond well to polychemotherapy.

**EPENDYMOMA:**

It accounts for 3- 5% of all brain tumors and third most common cns tumor in children. Commonly occurs in the infratentorial region. 10 % occurs in the spinal cord but can occur within the cerebral hemispheres according to Figerella et al[33] They are rare after 35 year according to CBTRUS[12]

**Gross**: Well demarcated, soft, grayish red tumor, necrosis and hemorrhage is present. In the spinal cord it is well defined and homogenous.

**Microscopy**: Moderately cellular gliomas with a monomorphic cells with round to oval nuclei with small nucleoli. Main histological features are perivascular pseudorosette, ependymal rosettes.

**Variants**: Cellular ependymoma, papillary ependymoma, clear cell ependymoma, tanycytic ependymoma and myxopapillary ependymoma.

World Health Organisation criteria for grading of ependymomas

| GRADE | HISTOLOGIC FEATURES |
|---|---|
| I | Low proliferative potential, discrete . Possibility of cure after surgical resection alone. |
| II | Infiltrating tumor mass, low mitotic activity. Recurrence is common and tend to progress to higher grades of malignancy |
| III | Increased mitotic activity, highly infiltrative and features of anaplasia. |
| IV | Mitotically active, massive areas of necrosis |

**Myxopapillary ependymoma** occurs exclusively in the region of the filum terminale, cauda equine , sacrum and extravertebral soft tissues.they have both fibrillar and epithelial cells. Prominent vascular hyalinisation and perivascular mucoid degeneration are characteristic features. Kliehues P et al[52] differential diagnosis may be chordoma and fibrous meningioma and schwannoma.

Other low grade ependymomas are epithelioid ependymomas, papillary ependymoma, tanycytic ependymoma.

## Grade IV ependymoma ( Ependymoblastoma):

It is characterised by conspicuous hypercellularity and ependymal rosettes. It is sometimes included under embryonal tumors . most cases occur in infants and children. It lacks the multinucleation and giant cells and has little or no endothelial proliferation. They infiltrate the leptomeninges and spread along the CSF.

**NEURONAL TUMORS:**

**GANGLIOGLIOMA/GANGLIOCYTOMA**: They are composed of intimately admixed neuronal and glial component and account for about 1% of all CNS tumors. The usual site for ganglioglioma is the temporal lobe accounting for over one third cases according to Blumke et al [7]. The Peak age of occurrence is between the 2 $^{nd}$ – 3$^{rd}$ decade. There is a male predominance according to Johnson JH et al [48] Gangliocytoma shows irregular groups of large multipolar neurons that shows dysplastic features. Stroma shows reactive glial cells and network of reticulin fibres.

**DESMOPLASTIC INFANTILE GANGLIOGLIOMA**:

**Gross**: Large tumor involving superficial cortex and leptomeninges.

**Microscopy**: It has a desmoplastic stroma with entrapped astrocytes and or neuronal cells.

**DYSEMBRYPLASTIC NEUROEPITHELIAL TUMOR**:

**Gross:** Intracortical multinodular firm mass

**Microscopy**: Typical glioneuronal element comprising microcystic spaces, oligodendrocyte like cells and floating neurons often associated with cortical dysplasias.

**CENTRAL NEUROCYTOMA**:

**Gross**:Greyish friable intraventricular tumor with calcified areas.

**Microscopy**: Composed of small regular polyhedral cells with honey comb like arrangement, round regular nucleus and pale cytoplasm. Microcalcifications are common.

**CHOROID PLEXUS PAPILLOMA**:

**Gross**: Circumscribed cauliflower like masses adherent to the ventricular wall but are well demarcated from the brain tissue

**Microscopy**: Well differentiated papillary neoplasm lined by cuboidal cells arranged in a single layer on the delicate papillary fronds. No mitosis is seen.

**CHOROID PLEXUS CARCINOMA**:

**Gross**: Solid invasive tumor with hemorrhage and necrosis.

**Microscopy:** Dysplastic cytological features include increased nuclear cytoplasmic ratio, mitotic activity, pseudostratified appearance and loss of nuclear polarity, cellular invasion into cerebral parenchyma with sheet like growth pattern.

**CHOROID GLIOMA OF THE THIRD VENTRICLE:**

**Microscopy**: Tumor is composed of clusters and cord of epithelial cells within a mucinous stroma. Stroma contain lymphoplasmacytic infiltration.

**PINEAL TUMORS:**

**PINEOBLASTOMA:**

**Gross**: Soft friable, poorly demarcated tumor with hemorrhage and or necrosis.

**Microscopy**: it is composed of patternless sheets of densely packed small cels with round to regular nuclei and scant cytoplasm. Homer Wright and Flexner Wintersteiner rosettes may be seen.

**PINEOCYTOMA**:

**Gross**: well circumscribed lesion, gray tan in colour.

**Microscopy:** composed of small uniform mature cells resembling pineocytes. Large pineocytomatous rosettes composed of abundant delicate tumor processes are seen.

**EMBRYONAL TUMORS**:

**MEDULLOBLASTOMA**:

Most common pediatric brain tumor of the posterior fossa. Mean age of occurrence is 7- 8 years. The male to female ratio is 1.5: 1 according to Roberts et al[95]

**Gross**: circumscribed, firm discrete mass

**Microscopy:** Densely packed cells with round to oval or carrot shaped hyperchromatic nuclei surrounded by scanty cytoplasm. Neuroblastic rosettes which consists of tumor cells arranged in a circular fashion around tangled

cytoplasmic processes are typical. Seeding of the CSF commonly give rise to drop metastasis in the lumbosacral spinal cord.

**Variants**: Desmoplastic/ nodular medulloblastoma, medulloblastoma with extensive nodularity , anaplastic medulloblastoma, large cell medulloblastoma.

**ATYPICAL RHABDOID / RHABDOID TERATOID TUMOR**:

It is grade IV tumor occurring in infants and young children < 3 years.

**Gross**: large cystic and hemorrhagic tumor.

**Microscopy**: Presence of rhabdoid cells with eccentrically placed vesicular nucleus, prominent nucleoli and globular eosinophilic paranuclear inclusions.[25]

**TUMORS OF THE CRANIAL AND PARASPINAL NERVES**:

**SCHWANNOMA:**

Bilateral schwannomas are associated with Neurofibroma -2. They are encapsulated tumors commonly occurs in the cerebello-pontine angle. When they are attached to the eighth cranial nerve the term acoustic neuroma is used.

**Microscopy**: they are composed of Schwann cells with characteristic densely cellular Antoni A areas with nuclear pallisading and verrocay bodies and hypocellular Antoni B areas.

**NEUROFIBROMA:**

NF arise and infiltrate within nerves and thus the neoplastic cells are intimately admixed with axons. Schwann cell, perineural cells, fibroblasts and mast cells are also found. There vessels are typically thin walled with a myxoid extracellular matrix.

**MALIGNANT PERIPHERAL NERVE SHEATH TUMOR**:

It has a very rare intracranial occurrence. They usually arise from a neurofibroma.tumar shows marked hypercellularity of spindle shaped cells with tapered ends, nuclear pleomorphism and abnormal mitosis. Necrosis indicates

grade IV tumor. Grade II tumor mimic neurofibroma but nuclei are darker and three times larger in size. S100 protein expression is markedly reduced.[25]

**MENINGIOMA:**

Meningiomas are tumors that arise from the leptomeningeal coverings of the brain and the spinal cord accounting for about 15 -20 % of all CNS tumors. there is a female preponderance[98]. Majority arise from the convexities and in the parasagittal location.Meningiomas are graded by the WHO into the following three grades .

| **GRADE I** | **GRADE II** | **GRADE III** |
|---|---|---|
| 0-3 mitosis / 10 hpf<br>2 or fewer atypical histological features | 4-19 mitosis/10 hpf (or)<br>≥ 3 foci of necrosis<br>Macronucleoli<br>Loss of architecture<br>Small cell change<br>Hypercellularity ( or)<br>Brain invasion ( or)<br>Clear cell or chordoid pattern. | ≥ 20 mitosis/10 hpf (or) papillary or rhabdoid pattern or otherwise overtly sarcoma or carcinoma like. |

Malignant meningiomas tend to recur after complete resection at a much higher rate (70% within 8 years). The extent of surgical resection is a critical determinant of survival. Extracranial metastasis from meningioma is rare(0.1%)

but occur more frequently (30%) in papillary meningioma according to Mathew JR et al[65].

## Benign meningioma:grade I

**Gross**: Spherical, lobulated firm and rubbery, usually well circumscribed dural based tumor. Tumors of the sphenoid wing grows as a flat carpet like masses termed ‘en plaque meningioma’

**Microscopy**: Tumor cells form lobules which are surrounded by thin collagenous septae. Cells are uniform with oval nuclei, even chromatin and eosinophilic cytoplasm forming syncytium.

**Variants**: Meningothelial, transitional, fibroblastic, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte rich, metaplastic (bone, cartilage,xanthomatous, myxoid,fat etc)

## Atypical meningioma: grade II

**Gross**: large tumor with cystic change

**Microscopy**: Sheeting pattern of tumor cells, brain invasion, necrosis, nuclear pleomorphism, prominent nucleoli and increased mitotic activity are features.

**Variants**: Chordoid and clear cell meningioma

## Malignant meningioma: grade III

**Microscopy**: Features similar to atypical meningioma but with more marked mitotic activity.

**Variants**: rhabdoid meningioma, papillary meningioma

**Rhabdoid meningioma(RM) :** It was first described in 1998 as an unusual variant of meningiomas. It has an increased proliferative activity and is classified as a WHO grade III meningioma. According to the literature, most RMs behave aggressively and have a very poor prognosis according to Perry A et al [82] It is important to recognize rhabdoid morphology in a meningioma early to help in both the diagnosis and understanding of its clinical course. The characteristic cytological appearance is the presence of eccentric lightly eosinophilic spherical cytoplasmic inclusions that compress the nucleus against the plasma membrane . The inclusion are composed of whorled aggregates of intermediate filaments.[82]

**HEMANGIOPERICYTOMA:**

**Gross:** solid well demarcated tumor, tendency to bleed during surgery, cut surface is fleshy greyish to red brown.

**Microscopy:** Highly monotonous cellular tumor composed of plump cells with scant cytoplasm accompanied by numerous small vascular spaces and dense network of reticulin fibres.

**HEMANGIOBLASTOMA:**

It often occurs in the setting of an inherited tumor predisposition syndrome with approximately 40 % of patients expressing features of von Hippel-Lindau (VHL) syndrome according to Convay et al[19] and Boughey AM et al.[8] It

commonly arises from the cerebellum and occurs more commonly in males in the second decade according to Silver ML et al.[108]

**Gross:** It is a sharply circumscribed tumor with a reddish brown to yellow colouration reflecting the rich vasculature and high lipid content according to Edward Hard et al[29]

**Microscopy:** Neoplastic elements are the stromal cells that have pale cytoplasm (neutral fat ) with vacuolated appearance and are found in the interstices between the ramifying vascular channels.

**MALIGNANT LYMPHOMA**:

**Gross:** single or multiple masses in the cerebrum, firm friable gray yellow with central necrosis.

**Microscopy**: lymphoma that diffusely infiltrates the brain parenchyma in the angiocentric pattern forming collar of tumor cells within concentric perivascular reticulin deposits.

**Variants:** B cell lymphoma, T cell lymphoma, Hodgkin disease, MALT lymphoma of the dura.

**PRIMARY CNS LYMPHOMA:**

It accounts for 2% of extranodal lymphomas and 1 % of intracranial tumors according to Robins and Cotran[96]. It occurs commonly in the

immunosuppressed individuals including those with AIDS, after transplants. They are mostly of the B cell origin. They are multifocal and relatively well defined in the brain parenchyma.

**Microscopy:** diffuse large cell lymphomas are the most common histological group. The tumor cells accumulate around the blood vessels. Reticulin stains shows the characteristic 'hooping' pattern with silver stains around individual tumor cells

**GERM CELL TUMORS**:

They are derived from primordial germ cells that migrate to the central neuraxis from the fetal yolk sac.

**Germinoma: Gross**: solid soft, friable tumor

**Microscopy**: Histologically similar to seminoma of the testis. They are composed of uniform cells resembling primitive germ cells with large vesicular nuclei, prominent nucleoli and lymphoplasmacytic cellular infiltrates. These tumors are PLAP ( Placental alkaline phosphatase) positive but not α-fetoprotien or β- HCG.

**Teratoma:**

**Gross**: mucous laden cysts, fat, chondroid nodules or bony spicules, rarely well fromed hair or teeth.

## Mature teratoma:

Composed of fully differentiated adult type tissue elements arranged in a pattern resembling normal tissue.

## Immature teratoma:

Composed of incompletely differentiated components resemling fetal tissues.

## Yolk sac tumor:

Composed of primitive appearing epithelial cells set in a loose, variably cellular and myxoid matrix resembling extraembryonic mesoblast. Eosinophilic hyaline globules may be seen occasionally

## Embryonal carcinoma:

Composed of large cells that proliferate in cohesive sheets and nests, form abortive papillae or gland like spaces. Tumor cells replicate the structure of the early embryo forming embryoid bodies

## Choriocarcinoma:

**Gross:** Extensive hemorrhagic and necrotic tissue

**Microscopy:** Characterised by extra-embryonic differentiation along the trophoblast. Diagnosis requires the identification of cytotrophoblastic elements and syncytiotrophoblastic giant cells.

**TUMORS OF THE SELLAR REGION:**

**CRANIOPHARYNGIOMA:**

**Gross:** Well demarcated solid tumor with cystic component, calcification. Cyst contains cholesterol rich, machine oil like, thick brownish yellow fluid.

**Microscopy:** Consists of strands of ameloblastic epithelium with peripheral palisading of nuclei. Diagnostic features are nodules of compact keratin and dystrophic calcification

**PITUITARY ADENOMA:**

**Gross:** well circumscribed soft tumor. Grey to yellow homogenous or granular.based on the size the adenomas are classified into microadenomas(<1 cm), macroadenomas (> 1 cm)and giant adenomas (>5 cm) according to Chako G et al [15]

**Microscopy**: There are two core features to distinguish adenomas from normal pituitary tissue are the loss of regular acinar pattern and cellular homogeneity according to De Lilleis[23]. The WHO categorises adenomas primarily by IHC staining for hormone products. The two features to distinguish adenomas from normal pituitary tissue are the absence of the regular acinar architecture and cellular homogeneity the ususal patterns of a pituitary adenoma are a sheet like pattern, trabecular, papillary, oncocytic, nested, ribboned, spindled or fascicular.

The clinical presentation of prolactinomas is sexually dimorphic with females presenting at younger ages with microadenomas (<1cm ) as they have a prolactin responsive breast and endometrial tissue, whereas males present at an older age with macroadenomas (>1 cm)

**METASTATIC TUMORS**:

They are the most common neoplasms accounting for more cases than the primary tumors according to Walker et al[121]. All metastasis reach the CNS by hematogenous route according to Gavriloc et al[35]. Most common primary tumor to metastasise to the CNS are from the lungs and the breast as per the study of Lagerward et al [55]

| Primary tumor | Frequency of metastasis to brain |
|---|---|
| Lung | 26%- 42% |
| Breast | 15%-25% |
| Skin ( melanoma) | 39% -92% |
| Kidney | 10%- 25% |
| Gastrointestinal tract | 5% -7% |

**Gross:** Occur as discrete round or well circumscribed grey white or tan masses. Tumor may be attached to the dura or leptomeninges and may form nodules.

**Microscopy**: metastasis are similar to those of the primary tumor from which they arise. Tumor necrosis is frequent with well defined borders with the adjacent parenchyma and displace rather than infiltrating the tissue as they enlarge.

**IMMUNOHISTOCHEMISTRY:**

## Ki- 67:

Various indices of cellular proliferative activity have been investigated. Mitotic counts only detect cells in the M phase, are dependent on the period of time between surgical removal and fixation of the specimen, and suffer from heterogeneous distribution and confusion between mitoses and nuclear pyknosis and karyorrhexis[10].

Counting nucleolar organiser regions (AgNORs) and 5-bromodeoxyuridine or tritiated thymidine labelling are also not practical in a routine situation. Bromodeoxyuridine ( BUdR) as a marker of tumor cell S phase fraction. BUdR fell out of favour because it required either injecting the patients with the compound prior to surgery or incubating a fresh tissue in BUdR containing solution immediadely upon removal. When Ki-67 labelling was developed it quickly took over the standard diagnostic role in determining proliferation potential in the tumor

Ki-67 recognises a proliferation specific nuclear antigen. The Ki-67 protein is a nuclear protein doublet, 345-395 kDa, playing a pivotal role in maintaining cell proliferation. Ki-67 is present in all non-G0 phases of the cell cycle. ‘Ki’ indicated the place of its origin- Kiel a town in Germany and 67 stands for the number of the clone of mouse antibody out of the 96 that was

isolated.  Beginning in the mid G1, the level increases through S and G2 to reach a peak in M. In the end of M, is is rapidly catabolized.

The Ki-67 labelling index (LI), i.e., the percentage of cells in a tissue staining for Ki-67, indicates the growth fraction. . There is a potential interest in using this marker in routine histopathology because it is simple and more rapid than the classic methods of evaluation of proliferating cells.

Grading of brain tumors are based on the observation of mitosis. The greatest disadvantage is that the brain biopsy material is often very  minimal and moreover may not be representative in most cases. Also crush artefacts may mimic mitosis in the sections. So a valid marker to highlight the exact number of cells undergoing mitosis is necessary and Ki -67 has proven to be the best immune marker in this study.

# *OBSERVATION AND RESULTS*

## OBSERVATIONS AND RESULTS

**INCIDENCE:**

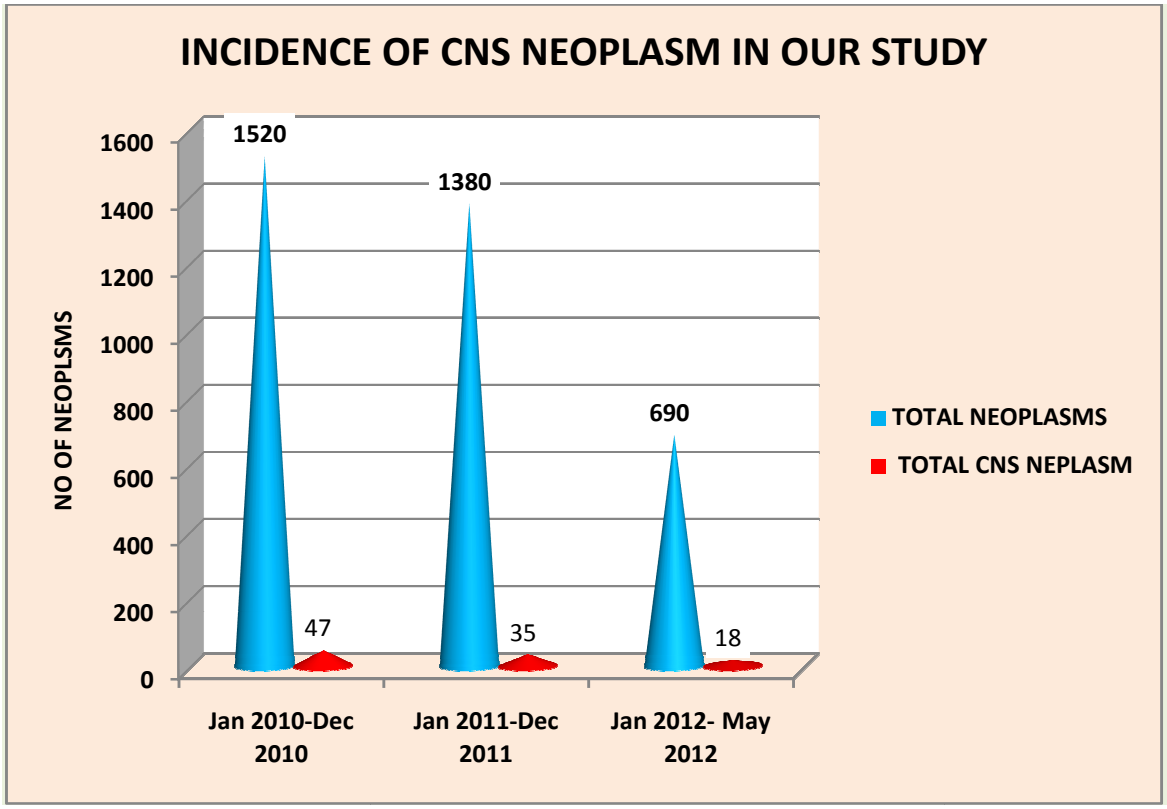
During the study period between January 2010 to May 2012, a total of 11050 general biopsy material were received in the department of pathology at Thanjavur medical college and Hospital Thanjavur. 100 central nervous system tumors were included in the study with an average incidence of 8.19% (chart 1)

**Table -1 Incidence of CNS neoplasms in our study**

| Period | Total no of specimens | Total neoplams | Total CNS neoplasms | Incidence |
|---|---|---|---|---|
| Jan 2010-Dec 2010 | 4556 | 1520 | 47 | 3.09% |
| Jan 2011- Dec 2011 | 4840 | 1380 | 35 | 2.5% |
| Jan 2012- May 2012 | 1654 | 690 | 18 | 2.6% |
| Total | 11050 | 3590 | 100 | 8.19 % |

Incidence of various CNS neoplasms in our study is shown in Table – 2 (chart –2) out of the 100 cases of CNS neoplasms, astrocytomas are the most common neoplasm constituting about 45% of cases, followed by meningiomas (23%), nerve sheath tumors (13 %),medulloblastoma(7 %) followed by pituitary adenomas constituting about 4 % . Ependymomas and hemangioblastomas, and secondary metastatic deposits constituted about 2% each and ganglioglioma and oligodendroglioma occurred in 1% of the total cases.

## CHART 1


INCIDENCE OF CNS NEOPLASM IN OUR STUDY
NO OF NEOPLSMS
1600
1400
1200
1000
800
600
400
200
0
1520
1380
690
47
35
18
Jan 2010-Dec 2010
Jan 2011-Dec 2011
Jan 2012- May 2012
TOTAL NEOPLASMS
TOTAL CNS NEPLASM

## Table 2

## Age wise incidence of CNS neoplasms

| Tumor | 1-10 yrs | 11-20 yrs | 21-30 yrs | 31-40 yrs | 41-50 yrs | 51-60 yrs | 61-70 yrs | 71-80 yrs | Total |
|---|---|---|---|---|---|---|---|---|---|
| Astrocytoma | - | 4 | 10 | 11 | 11 | 7 | 1 | 1 | 45 |
| Meningioma | 1 | - | 2 | 7 | 4 | 5 | 3 | 1 | 23 |
| Nerve sheath tumor | 1 | 2 | 2 | 3 | 3 | 1 | 1 | - | 13 |
| Medulloblastoma | 3 | 4 | - | - | - | - | - | - | 7 |
| Pituitary adenoma | 1 | - | - | 2 | - | - | 1 | - | 4 |
| Ependymoma | - | - | - | 1 | - | 1 | - | - | 2 |
| Hemangioblastoma | - | - | 1 | - | 1 | - | - | - | 2 |
| Metastasis | - | - | - | 1 | 1 | - | - | - | 2 |
| Ganglioglioma | - | - | - | - | 1 | - | - | - | 1 |
| Oligodendroglioma | - | - | 1 | - | - | - | - | - | 1 |
| **Total** | **6** | **10** | **16** | **25** | **21** | **15** | **6** | **2** | **100** |

Table 2 also shows the age wise incidence of CNS neoplasms. In the age group of 1-10 yrs medulloblastoma is the most common neoplasm. Astrocytomas are common in the fourth and the fifth decade (49%). Meningiomas are also common in the fourth decade (30%). In this study more number of medulloblastomas occurred in the second decade(57%).

## CHART -2

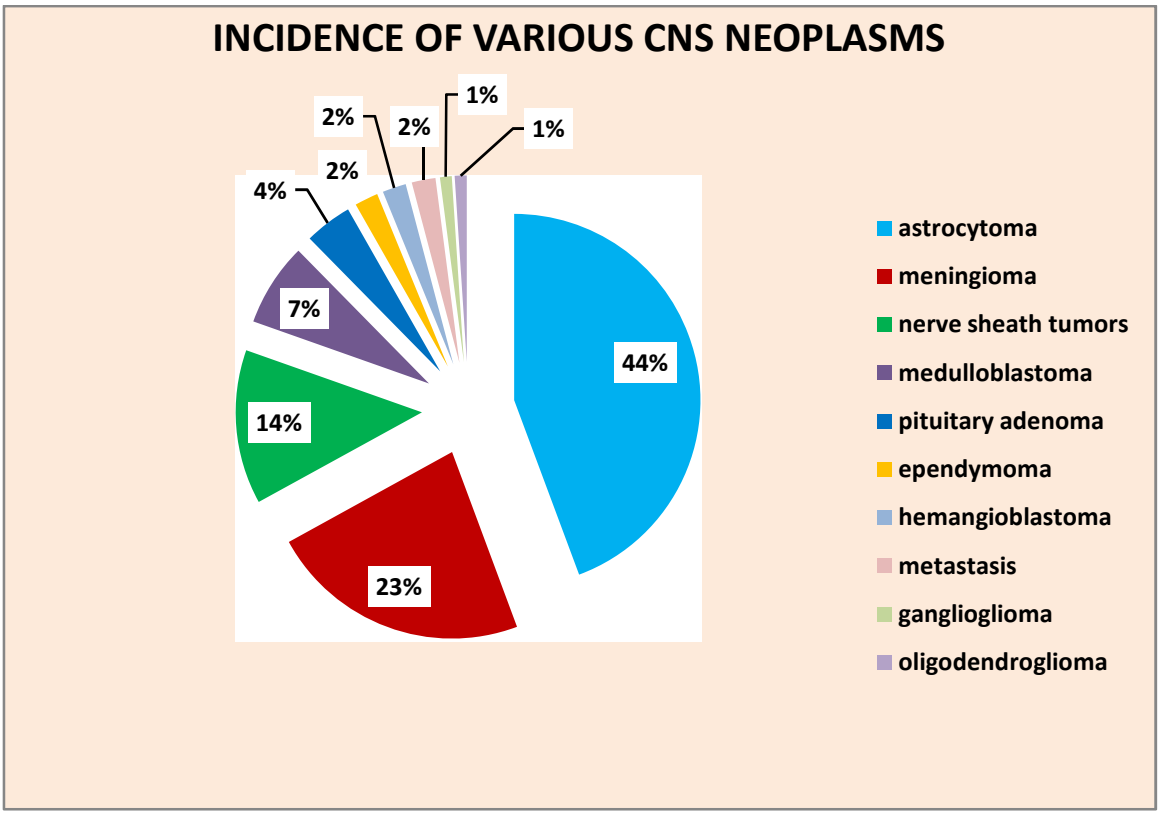

INCIDENCE OF VARIOUS CNS NEOPLASMS
44%
23%
14%
7%
4%
2%
2%
2%
1%
1%
astrocytoma
meningioma
nerve sheath tumors
medulloblastoma
pituitary adenoma
ependymoma
hemangioblastoma
metastasis
ganglioglioma
oligodendroglioma

**Table -3**
**Overall sites of occurrence of CNS neoplasms**

| Site | No. Of cases | Percentage |
|---|---|---|
| Frontal lobe | 28 | 28% |
| Parietal lobe | 23 | 23% |
| Temporal lobe | 13 | 13% |
| Spinal cord | 11 | 11% |
| Posterior fossa | 8 | 8% |
| CP angle | 6 | 6% |
| Pituitary fossa | 5 | 5% |
| Sphenoid wing | 3 | 3% |
| Occipital lobe | 3 | 3% |

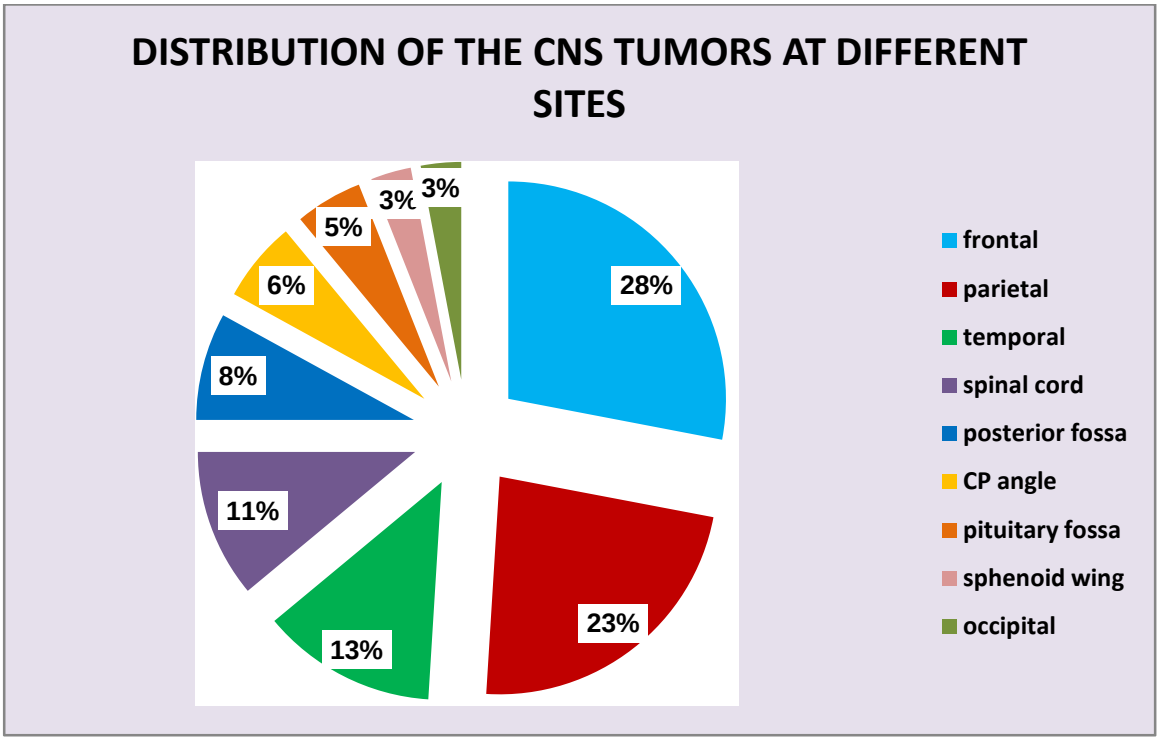
From the above table -3 (chart -3) we observe that the most common site of occurrence of CNS tumors is in the frontal lobe (28%) followed by the parietal lobe(23%)

**Table – 4**

**Age and sex wise incidence of CNS tumors**

| Age | Male | Female | Total |
|---|---|---|---|
| 1-10 yrs | 2 | 4 | 6 |
| 11-20 yrs | 7 | 3 | 10 |
| 21-30 yrs | 9 | 7 | 16 |
| 31-40 yrs | 10 | 14 | 24 |
| 41-50 yrs | 13 | 7 | 20 |
| 51-60 yrs | 7 | 8 | 15 |
| 61-70 yrs | 5 | 2 | 7 |
| 71-80 yrs | 1 | 1 | 2 |
| **Total** | **54** | **46** | **100** |

## CHART- 3




## CHART -4

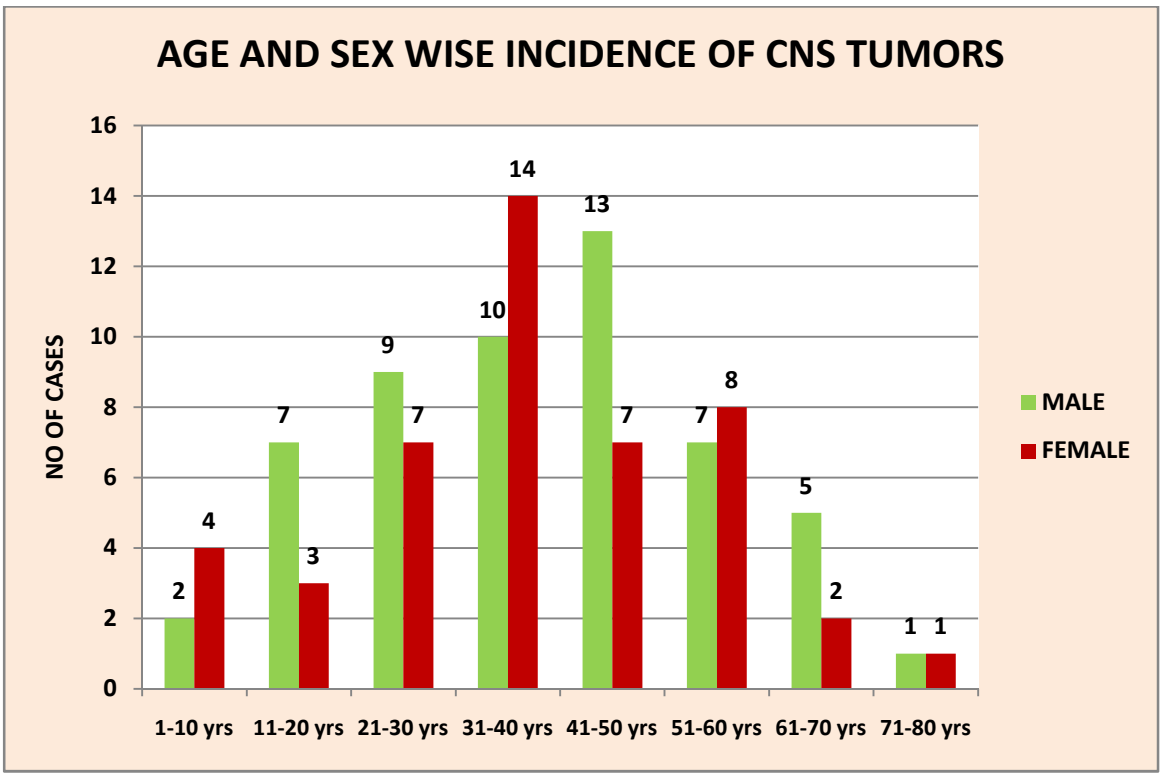


Table-4 (chart 4) shows that most common age group of occurrence of CNS tumors were in the age group of 31- 40 years(24%) followed by 41-50 years age group. Least number of cases occurred in the 70 -80 years age group (2%) followed by 1-10 years age group (6%). There was a definite overall male preponderance( 54 %) in our study.

**GRADING**

Grading is done for all tumors according to the WHO 2007 norms. This includes the neuroepithelial, meningeal, neural and pituitary tumors. The overall occurrence of various grades of neoplasm with respect to age is illustrated in the following table.

**Table-5**

**WHO grading of all CNS neoplasms with respect to age**

| Grade | 1-10 yrs | 11-20 yrs | 21-30 yrs | 31-40 yrs | 41-50 yrs | 51-60 yrs | 61-70 yrs | 71-80 yrs | Total |
|---|---|---|---|---|---|---|---|---|---|
| I | 2 | 2 | 4 | 10 | 9 | 7 | 6 | 1 | 42 |
| II | - | - | 3 | 6 | 2 | 2 | - | - | 13 |
| III | 1 | 1 | 6 | 4 | 1 | 3 | 1 | - | 16 |
| IV | 3 | 7 | 3 | 3 | 8 | 4 | - | 1 | 29 |

The above table -5 (chart -5) indicates that the grade I tumors are the most common followed by grade IV tumors. Grade I and grade II tumors commonly occurred in the 31- 40 age group and grade IV tumors had a bimodal peak in the second and the fourth decade.

## CHART – 5

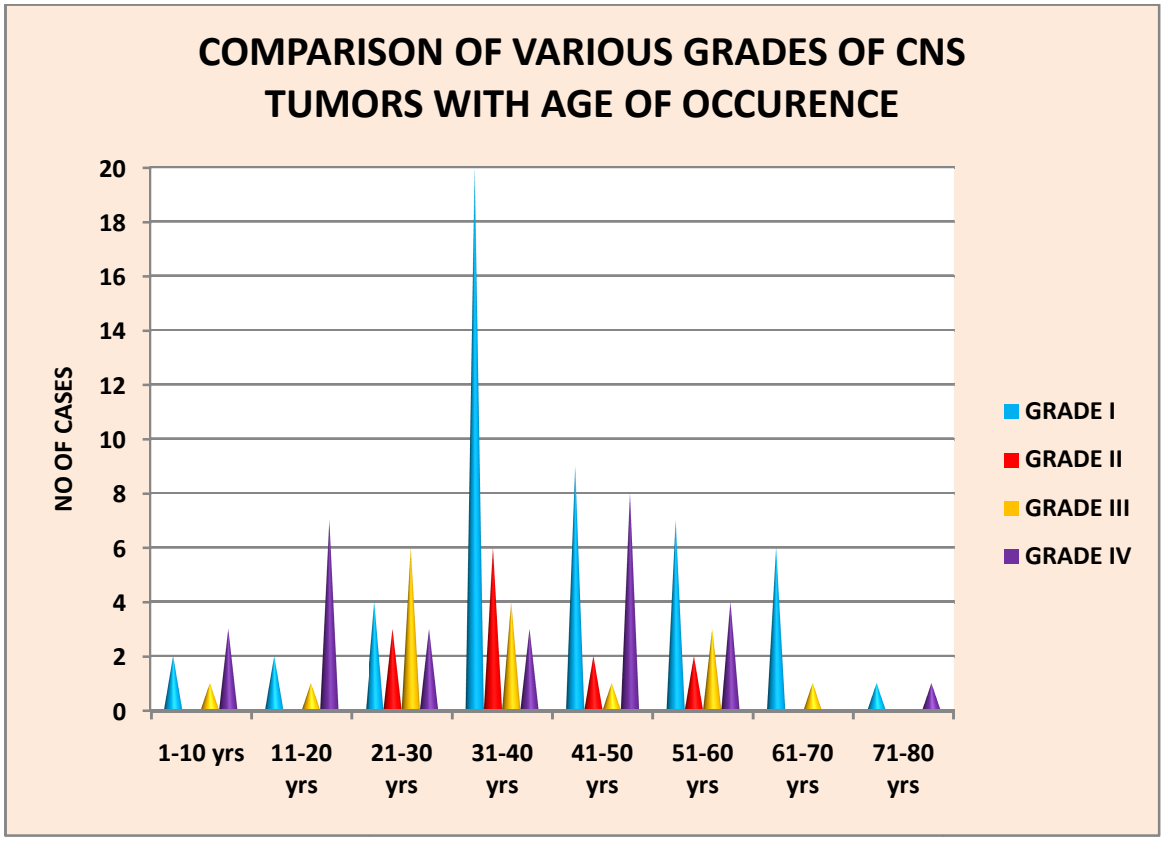

COMPARISON OF VARIOUS GRADES OF CNS TUMORS WITH AGE OF OCCURENCE
NO OF CASES
20
18
16
14
12
10
8
6
4
2
0
1-10 yrs
11-20 yrs
21-30 yrs
31-40 yrs
41-50 yrs
51-60 yrs
61-70 yrs
71-80 yrs
GRADE I
GRADE II
GRADE III
GRADE IV

**Table -6**

**Grading and sex wise incidence of CNS neoplasms.**

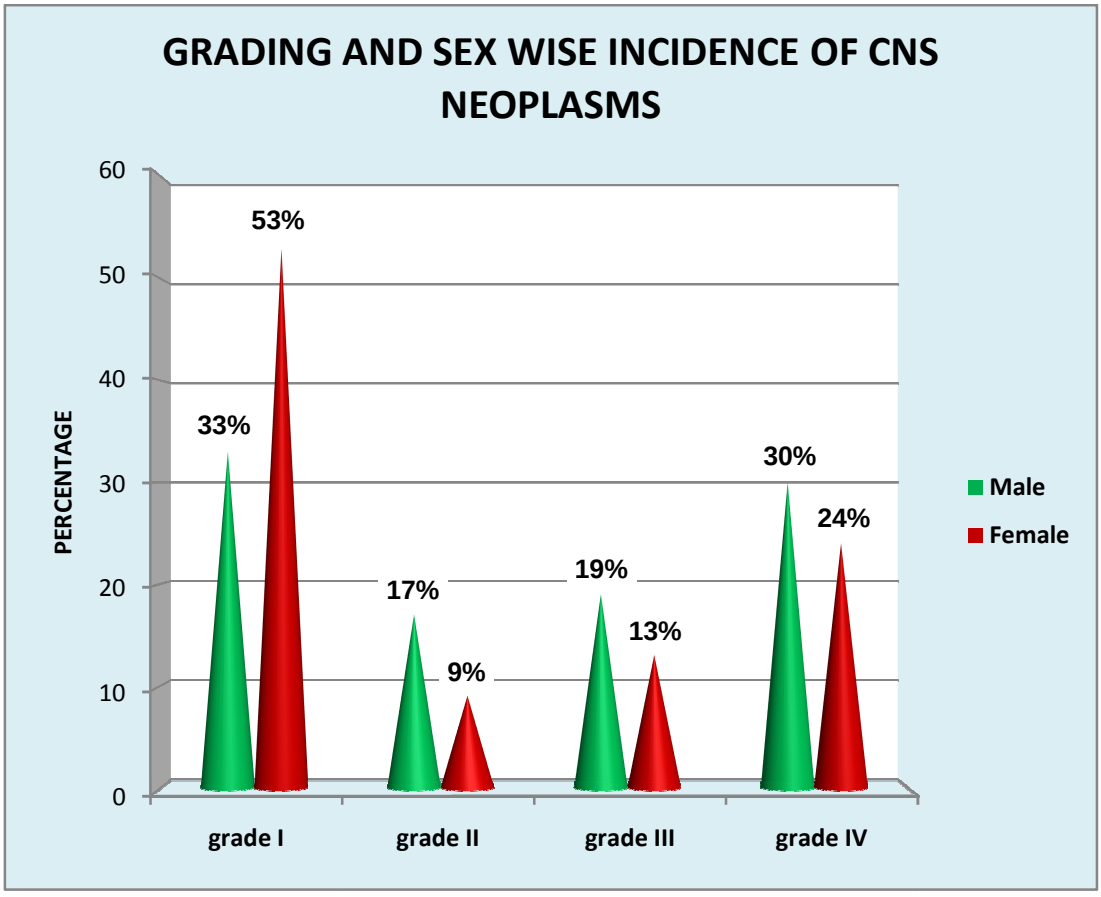
| Grade | Male | Percentage | Female | Percentage |
|---|---|---|---|---|
| **I** | 18 | 33% | 24 | 53.3% |
| **II** | 9 | 16.98% | 4 | 8.8% |
| **III** | 10 | 18.86% | 6 | 13.3% |
| **IV** | 17 | 31.48% | 12 | 26.08% |
| **Total** | **54** | **54.08%** | **46** | **45.91%** |

Our study showed a overall increase in occurrence of the CNS tumors in the male population (54 %). The above table -6 (chart-6) shows that the females outnumber the males in the grade I tumors (24 cases,53.3%) alone. Grade II( 9 cases 16.98 %), grade III (10 cases, 18.86%) and grade IV (17 cases,31.48 %) tumors are common in males.

**WHO grading for astrocytomas**

Astrocytomas were graded according to the WHO criteria of cellularity, nuclear atypia, mitosis and microvascular proliferation/necrosis as showin the table -7 below

## CHART -6


GRADING AND SEX WISE INCIDENCE OF CNS NEOPLASMS
PERCENTAGE
60
50
40
30
20
10
0
53%
33%
17%
9%
19%
13%
30%
24%
grade I
grade II
grade III
grade IV
Male
Female

# Table -7

# WHO grading of Astrocytoma

| S.no | Pathology no | HPE diagnosis | Increased cellularity | Nuclear atypia | Mitosis | Microvascular proliferation& necrosis | Grade |
|---|---|---|---|---|---|---|---|
| 1 | 261/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 2 | 326/10 | Diffuse astrocytoma | + | + | - | - | II |
| 3 | 433/10 | Anaplastic astrocytoma | + | + | + | - | III |
| 4 | 555/10 | Anaplastic astrocytoma | + | + | + | - | III |
| 5 | 881/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 6 | 915/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 7 | 1149/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 8 | 1399/10 | Diffuse astrocytoma | + | + | - | - | II |
| 9 | 1437/10 | Fibrillary astrocytoma | + | - | - | - | I |
| 10 | 1621/10 | Diffuse astrocytoma | + | + | - | - | II |
| 11 | 1660/10 | Diffuse astrocytoma | + | + | - | - | II |
| 12 | 1831/10 | Anaplastic astrocytoma | + | + | + | - | III |
| 13 | 2141/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 14 | 2236/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 15 | 2307/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 16 | 2401/10 | Diffuse astrocytoma | + | + | - | - | II |
| 17 | 2814/10 | Diffuse astrocytoma | + | - | - | - | I |
| 18 | 3683/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 19 | 3686/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 20 | 3990/10 | Glioblastoma multiforme | + | + | + | + | IV |
| 21 | 4128/10 | Anaplastic astroctoma | + | + | + | - | III |
| 22 | 233/11 | Diffuse astrocytoma | + | + | - | - | II |
| 23 | 272/11 | Diffuse astrocytoma | + | + | - | - | II |
| 24 | 504/11 | Anaplstic astrocytoma | + | + | + | - | III |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 25 | 734/11 | Glioblastoma multiforme | + | + | + | + | IV |
| 26 | 1383/11 | Glioblastoma multiforme | + | + | + | + | IV |
| 27 | 1951/11 | Anaplastic astrocytoma | + | + | + | - | III |
| 28 | 2030/11 | Anaplastic astrocytoma | + | + | + | - | III |
| 29 | 2484/11 | Diffuse astrocytoma | + | - | - | - | I |
| 30 | 2630/11 | Anaplastic astrocytoma | + | + | + | - | III |
| 31 | 3523/11 | Anaplastic astrocytoma | + | + | + | - | III |
| 32 | 3730/11 | Glioblastoma multiforme | + | + | + | + | IV |
| 33 | 3841/11 | Glioblastoma multiforme | + | + | + | + | IV |
| 34 | 4327/11 | Glioblastoma multiforme | + | + | + | + | IV |
| 35 | 4535/11 | Gliosarcoma | + | + | + | + | IV |
| 36 | 215/12 | Glioblastoma multiforme | + | + | + | + | IV |
| 37 | 295/12 | Diffuse astrocytoma | + | + | - | - | II |
| 38 | 338/12 | gliosarcoma | + | + | + | + | IV |
| 39 | 539/12 | Diffuse astrocytoma | + | + | - | - | II |
| 40 | 628/12 | Diffuse astrocytoma | + | + | - | - | II |
| 41 | 819/12 | Glioblastoma multiforme | + | + | + | + | IV |
| 42 | 934/12 | Anaplastic astrocytoma | + | + | + | - | III |
| 43 | 1380/12 | Anaplastic astrocytoma | + | + | + | - | III |
| 44 | 1475/12 | Anaplastic astrocytoma | + | + | + | - | III |
| 45 | 1827/12 | Glioblastoma multiforme | + | + | + | + | IV |

All the astrocytomas were graded meticulously by light microscopy and classical features of Glioblastoma like glomeruloid endothelial proliferation and pseudopalisading necrosis were observed.

**Table -8**

**Grade and sex wise incidence of astrocytoma**

| Grade | Male | Female | Total |
|---|---|---|---|
| **I** | 2 | 1 | 3 (7%) |
| **II** | 7 | 3 | 10 (22%) |
| **III** | 9 | 3 | 12 (27%) |
| **IV** | 11 | 9 | 20 (44%) |
| **Total** | **29 (64.4%)** | **16 (35.5%)** | **45** |

The above table-8 (chart-7) show that there is an male preponderance in all grades of astrocytomas . Also in this study a higher incidence of grade IV astrocytomas was noted (44 %) followed by grade III (27%), grade II (22%) and grade I (7%) asrocytoma (fig 2-5). Two cases of gliosarcoma(fig 6) which is considered to be a variant of glioblastoma multiforme was included under grade IV astrocytoma

## CHART -7

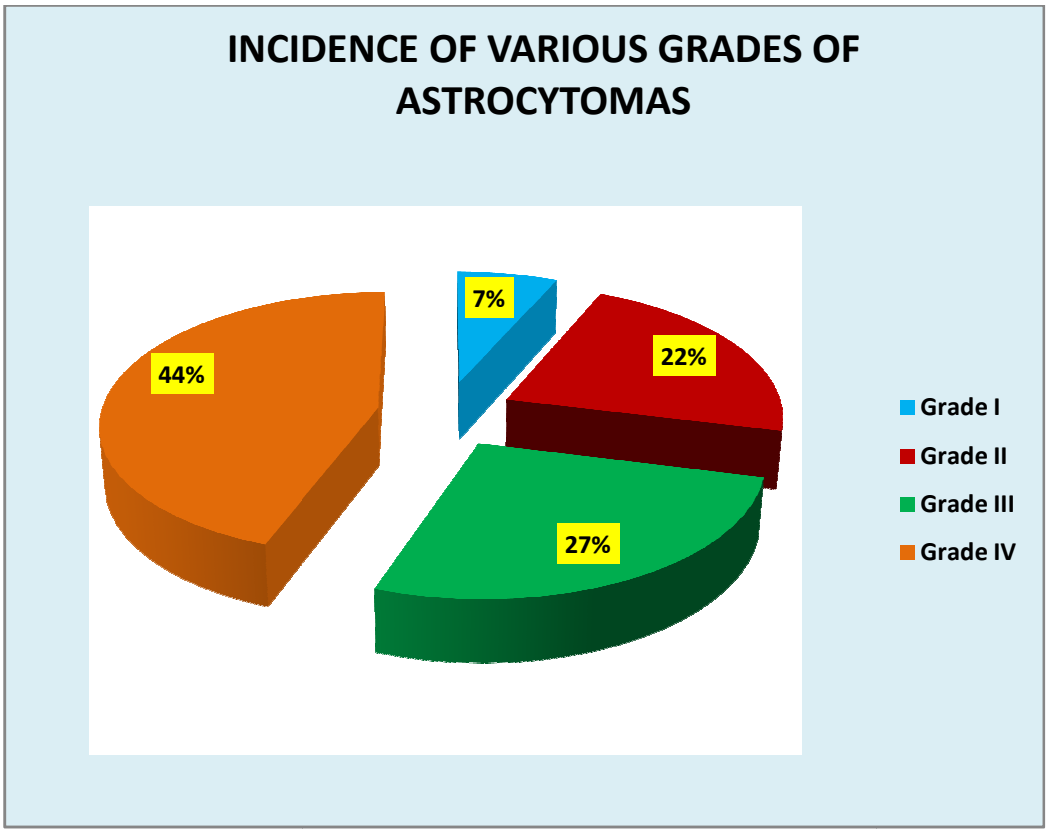
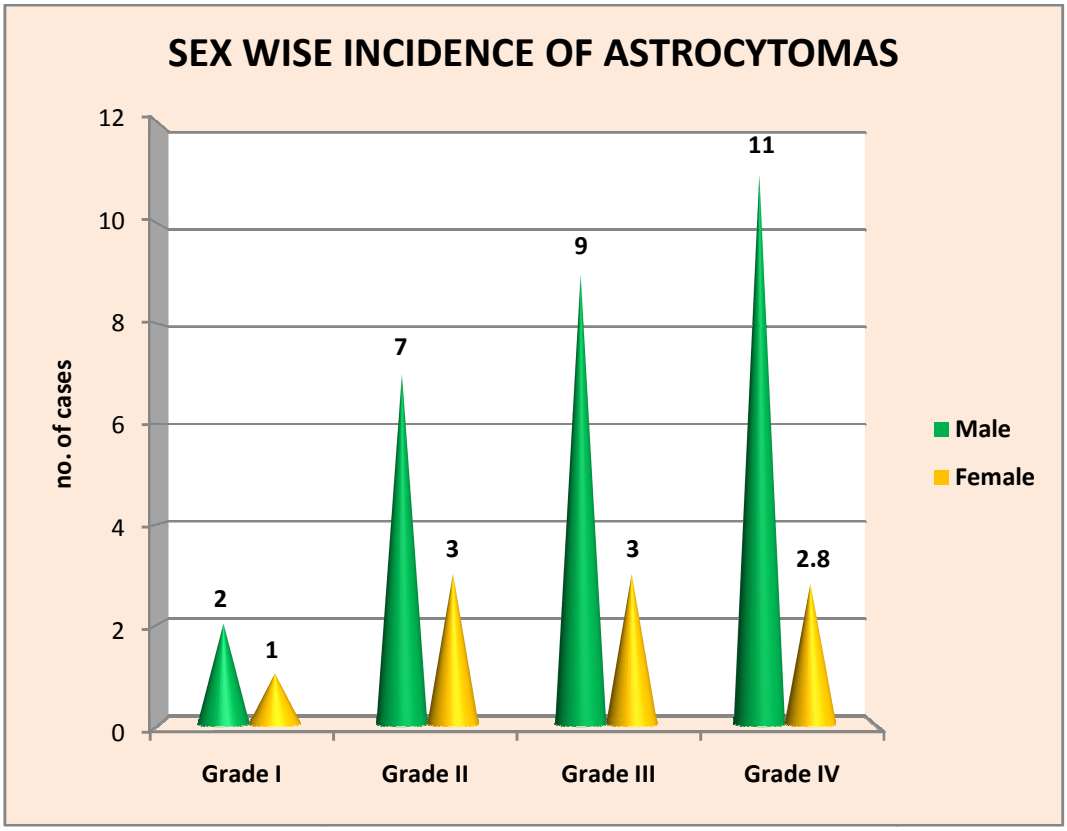

INCIDENCE OF VARIOUS GRADES OF ASTROCYTOMAS
7%
22%
27%
44%
Grade I
Grade II
Grade III
Grade IV

**Table – 9**
**Grade and age wise incidence of astrocytoma**

| Grade | 1-10 yrs | 11-20 yrs | 21-30 yrs | 31-40 yrs | 41-50 yrs | 51-60 yrs | 61-70 yrs | 71-80 yrs |
|---|---|---|---|---|---|---|---|---|
| **I** | - | - | - | 3 | 1 | - | - | - |
| **II** | - | - | 2 | 3 | 1 | 2 | - | - |
| **III** | - | 1 | 5 | 1 | 2 | 2 | 1 | - |
| **IV** | - | 3 | 3 | 4 | 7 | 3 | - | 1 |
| **Total** | 0 | 4 | 10 | 11 | 11 | 7 | 1 | 1 |

The above table- 9 (chart-8) shows that overall all grades of astrocytomas are common in the third and the fourth decade followed by second decade in our study. There were no cases in the first decade and just one case each in the sixth and the seventh decade.

## CHART -8


SEX WISE INCIDENCE OF ASTROCYTOMAS
no. of cases
12
10
8
6
4
2
0
2
1
7
3
9
3
11
2.8
Grade I
Grade II
Grade III
Grade IV
Male
Female

## TABLE -10
## WHO grading of meningioma

| S.No | Patho no. | HPE diagnosis | Increased cellularity | Sheeting pattern | Increased mitosis | grading |
|---|---|---|---|---|---|---|
| 1. | 263/10 | Meningothelial meningioma | N | - | - | I |
| 2. | 265/10 | Transitional meningioma | N | - | - | I |
| 3 | 393/10 | Transitional meningioma | N | - | - | I |
| 4 | 577/10 | Anaplastic meningioma | ↑ | + | >20/10 hpf | III |
| 5 | 667/10 | Meningothelial meningioma | N | - | - | I |
| 6 | 1439/10 | Meningothelial meningioma | N | - | - | I |
| 7. | 1967/10 | Anaplastic meningioma | ↑ | + | >20/10 hpf | III |
| 8 | 3353/10 | Angiomatous meningioma | N | - | - | I |
| 9. | 3741/10 | Psammomatous meningioma | N | - | - | I |
| 10. | 3822/10 | Transitional meningioma | N | - | - | I |
| 11 | 4258/10 | Meningothelial meningioma | N | - | - | I |
| 12. | 834/11 | Transitional meningioma | N | - | - | I |
| 13. | 1561/11 | Atypical meningioma | ↑ | + | >4/10 hpf | II |
| 14 | 1839/11 | Transitional meningioma | N | - | - | I |
| 15 | 2771/11 | Transitional meningioma | N | - | - | I |
| 16 | 2936/11 | Meningothelial meningioma | N | - | - | I |
| 17 | 3380/11 | Meningothelial meningioma | N | - | - | I |
| 18 | 3401/11 | Meningothelial meningioma | N | - | - | I |
| 19 | 4113/11 | angiomatous meningioma | N | - | - | I |
| 20 | 4670/11 | Transitional meningioma | N | - | - | I |
| 21 | 299/12 | Transitional meningioma | N | - | - | I |
| 22 | 909/12 | Meningothelial meningioma | N | - | - | I |
| 23 | 1261/12 | Rhabdoid meningioma | ↑ | + | >20/10 hpf | III |

**Table -11**
**Grade and sex wise incidence of meningioma**

| Grade | Male | Female | Total |
|---|---|---|---|
| **I** | 2 | 17 | 19 (82%) |
| **II** | 1 | - | 1 (5%) |
| **III** | - | 3 | 3 (13%) |
| **Total** | **3 (13%)** | **20(87%)** | **23** |

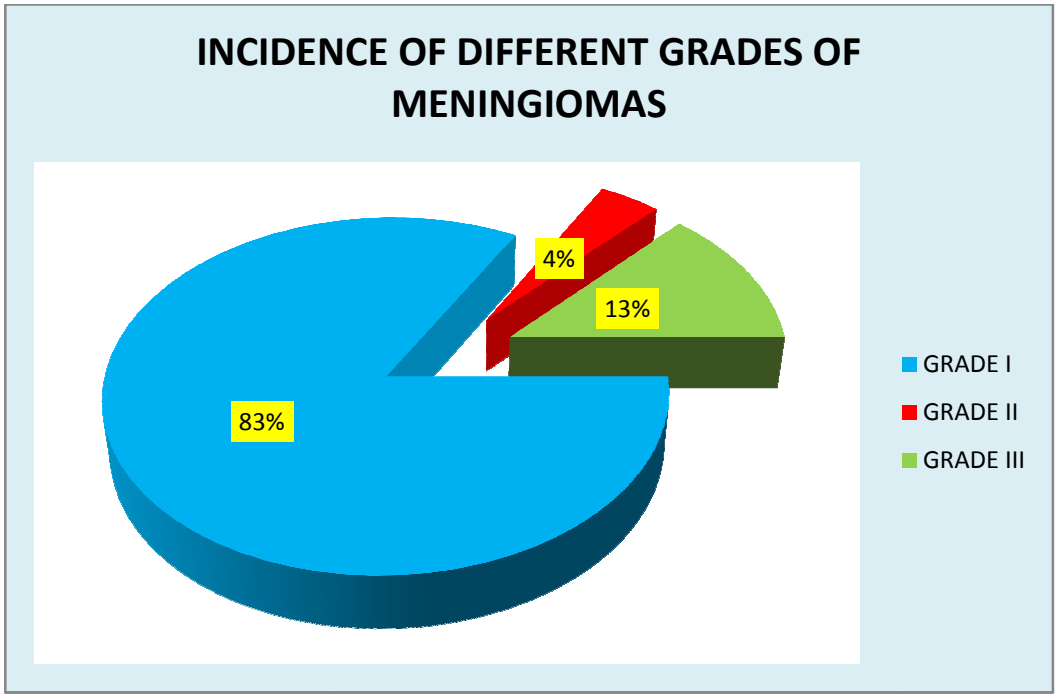
The above table- 11( chart- 10) shows that there are about 87% of meningiomas occurring in females outnumbering the males(13%). Grade I tumors constitute about 18 cases(82 %) and grade III tumors occurring in 3 cases(13%) ( fig- 9,10) including a case of rhabdoid meningioma. (fig - 11)

**Table -12**
**Grade and age of various meningiomas**

| Age | Grade I | Grade II | Grade III | Total |
|---|---|---|---|---|
| **1-10 yrs** | - | - | 1 | 1 |
| **11-20 yrs** | - | - | - | - |
| **21-30 yrs** | 1 | - | 1 | 2 |
| **31-40 yrs** | 4 | 1 | 1 | 6 |
| **41-50 yrs** | 5 | - | - | 5 |
| **51-60 yrs** | 5 | - | - | 5 |
| **61-70 yrs** | 3 | - | - | 3 |
| **71-80yrs** | 1 | - | - | 1 |
| **Total** | **19(82.6%)** | **1(4.4%)** | **3(13%)** | **23** |

Most common age group of occurrence of meningiomas were in the third decade( 6 cases) followed by fourth and fifth decade. There were no case in the 11-20 age group and only a single case occurred in the 1-10 yrs and 71-80 yrs age group.

## CHART - 9




## CHART 10

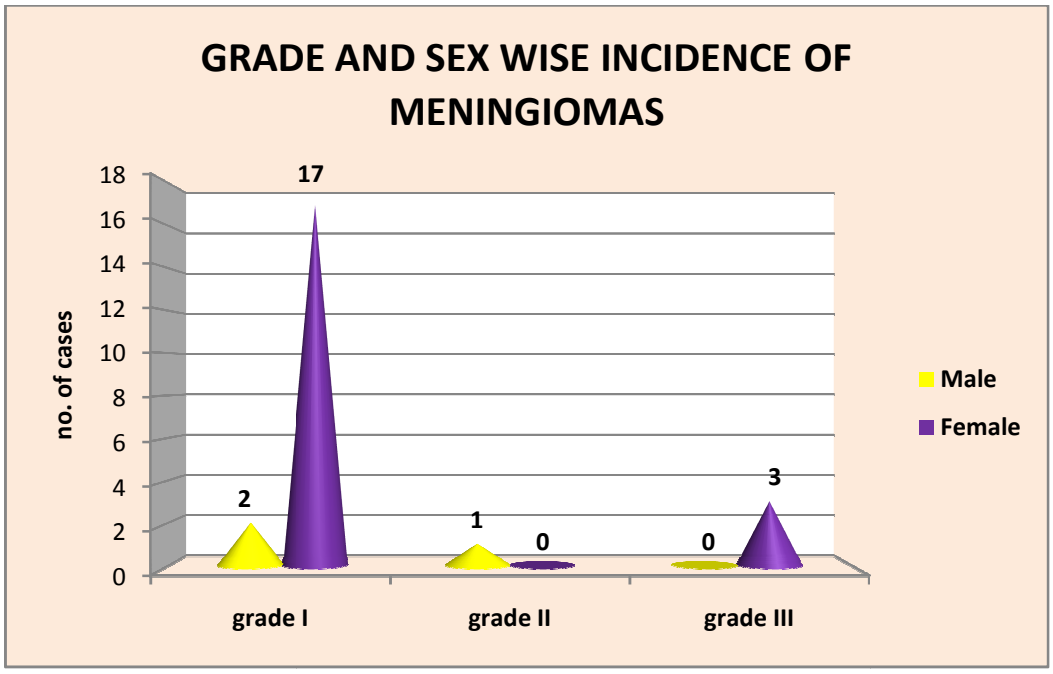


**Table -13**
**WHO grading of neural tumors**

| S.no | Patho no. | Age/ sex | HPE diagnosis | Site | Mitosis | Necrosis | Grade |
|---|---|---|---|---|---|---|---|
| 1. | 479/10 | 19/M | Schwannoma | D9-D10 | - | - | I |
| 2. | 1374/10 | 48/F | Schwannoma | Cerebello-pontine angle | - | - | I |
| 3. | 3859/10 | 38/F | Schwannoma | Cerebello-pontine angle | - | - | I |
| 4. | 4211/10 | 42/M | Schwannoma | Cerebello-pontine angle | - | - | I |
| 5. | 100/11 | 65/M | Schwannoma | L3-L4 | - | - | I |
| 6. | 723/11 | 9/F | Neurofibroma | D1-D3 | - | - | I |
| 7. | 2032/11 | 26/M | Neurofibroma | C5-C6 | - | - | I |
| 8. | 2890/11 | 55/F | Neurofibroma | L1-L2 | - | - | I |
| 9. | 3055/11 | 35/F | MPNST | D1-D3 | | | II |
| 10 | 3303/11 | 30/M | Schwannoma | Cerebello-pontine angle | - | - | I |
| 11 | 390/12 | 20/M | Schwannoma | D7-D8 | - | - | I |
| 12. | 500/12 | 49/M | Schwannoma | Cerebello-pontine angle | - | - | I |
| 13 | 1537/12 | 40/M | Schwannoma | Cerebello-pontine angle | - | - | I |

Tumors of the cranial and spinal nerves constitute about 13% of cases in this study. Schwannomas are the commonly reported tumor(9 cases) followed by neurofibroma. Only one case of low grade MPNST was reported(fig- 17). Most of the tumors occurred in the cerebello- pontine angle (6 cases) and the remaining occurred in the spine.(chart -11)

## CHART -11

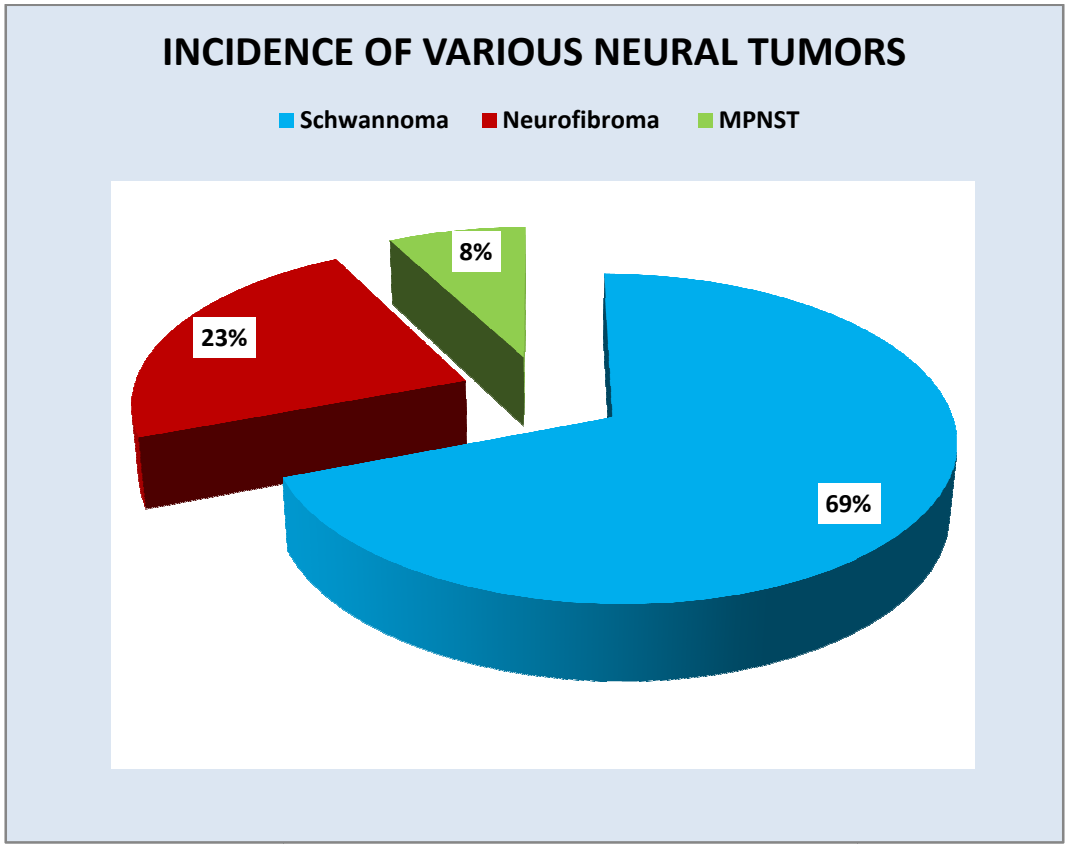

INCIDENCE OF VARIOUS NEURAL TUMORS
Schwannoma
Neurofibroma
MPNST
8%
23%
69%

**TABLE – 14**

**Age wise incidence of neural tumors**

| AGE IN YRS | MALE | FEMALE |
|---|---|---|
| 1-10 | - | 1 |
| 11-20 | 2 | - |
| 21-30 | 2 | - |
| 31-40 | 1 | 2 |
| 41-50 | 2 | 1 |
| 51-60 | 1 | - |
| 61-70 | 1 | - |
| Total | 9 | 4 |

Also it is noted that the sex wise incidence is more favourable towards males ( 9 cases). The neural tumors had a wide distribution with respect to age with the maximum occurrence in the 30- 50 yrs age group. Most of the neural tumors occurred in the spinal cord except one case of meningioma and one case of myxopaillary ependymoma

**PEDIATRIC BRAIN TUMORS**

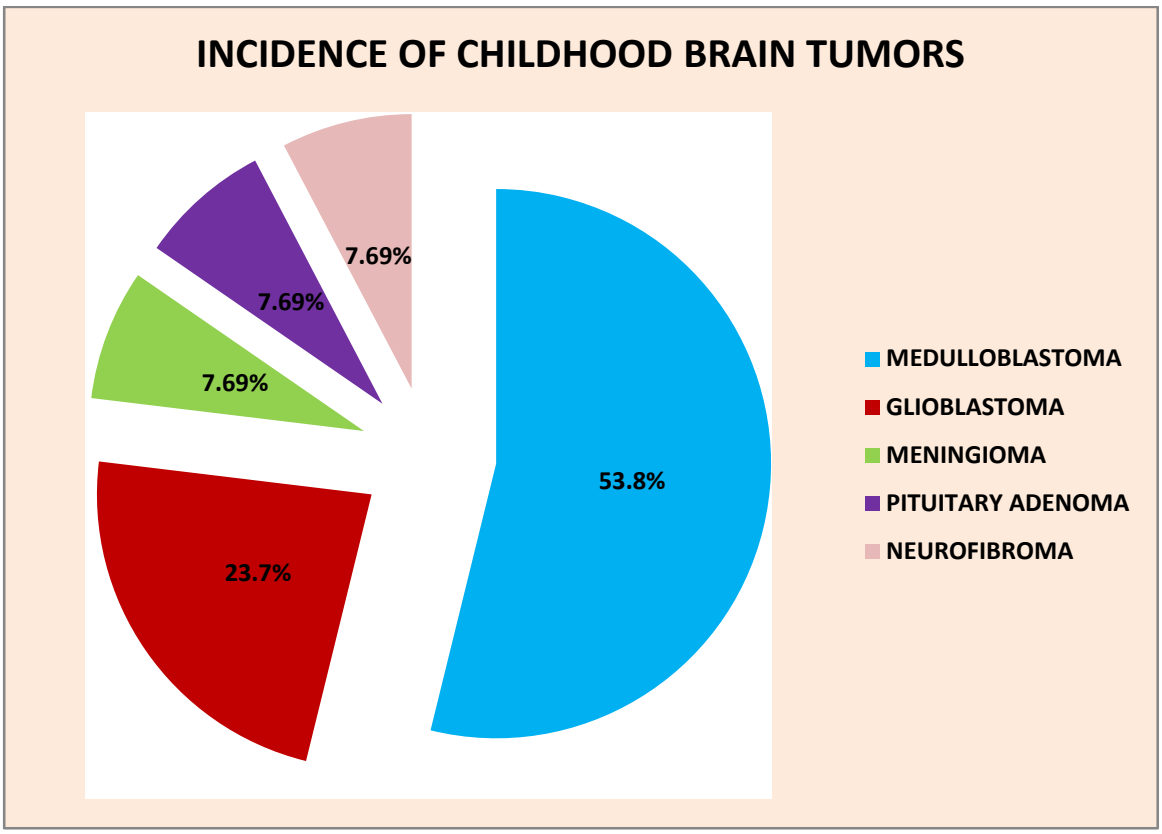
## TABLE 15

## Incidence of brain tumors in children

| s.no | Patho no | Age/sex | Histological diagnosis | SITE | grade |
|---|---|---|---|---|---|
| 1 | 478/10 | 16/M | Medulloblastoma | Posterior fossa | IV |
| 2 | 2487/10 | 7/M | Medulloblastoma | posterior fosa | IV |
| 3 | 2526/10 | 14/M | Medulloblastoma | Posterior fossa | IV |
| 4 | 2738/10 | 11/M | Medulloblastoma | Posterior fossa | IV |
| 5 | 3482/10 | 10/F | Medulloblastoma | Posterior fossa | IV |
| 6 | 3739/10 | 6/F | Medulloblastoma | Posterior fossa | IV |
| 7 | 723/11 | 9/F | Neurofibroma | D1-D3 | I |
| 8 | 1167/11 | 12/M | Medulloblastoma | Posterior fossa | IV |
| 9 | 1383/11 | 13/F | GBM | Frontal lobe | IV |
| 0 | 4535/11 | 15/F | Gliosarcoma | Frontal lobe | IV |
| 11 | 338/11 | 15/F | Gliosarcoma | Frontal lobe | IV |
| 12 | 1261/12 | 10/F | Rhabdoid meningioma | Temporal lobe | III |

Distribution of childhood brain tumors are shown in chart - 12.Medulloblstoma was the next common tumor reported. We had 7 cases ( 7%) (fig 16), all of them occurred in the pediatric age group ( 0-15 years). All

## CHART – 12


INCIDENCE OF CHILDHOOD BRAIN TUMORS
7.69%
7.69%
7.69%
53.8%
23.7%
MEDULLOBLASTOMA
GLIOBLASTOMA
MENINGIOMA
PITUITARY ADENOMA
NEUROFIBROMA

tumors were from the posterior fossa. Males ( 5 cases) outnumbered the females (2 cases)..

There were four cases(4%) of pituitary adenoma (fig 13)in our study with equal male to female ratio. All the four cases occurs in the sellar region. Two cases were in the 30 -40 age group but the other two were in the extremes of age. One in a 10 yrs old girl and the other in a 70 years male.(chart -12)

Two cases of ependymoma(2%) was reported(fig 18). One was a classical ependymoma in a 32 years male in the frontal lobe. Another was a case of myxopapillary ependymoma(fig 19) that occurred in the classical lumbosacral location of a 55 years old man.

There were two cases( 2%) of hemangioblastoma(fig 15) in our study. One tumor occurred in a 23 years old male in the posterior fossa. And the other was in a 65 years male in the parietal lobe which was a rare site.

There was one case each of oligodendroglioma(fig 14) and ganglioglioma (fig 12) (1%). Oligodendroglioma was reported in a 30 years old male in the parietal region and ganglioglioma was reported in a 42 years old male from the frontal lobe.

In our study we had two cases(2%) of metastatic deposit(fig 20) in the brain. Both the cases were between 40 -45 years and were adenocarcinomatous deposits. The primary was found in the GIT for both cases

## IMMUNOHISTOCHEMISTRY

## TABLE – 16

## KI- 67 LABELLING INDEX OF VARIOUS CNS NEOPLASMS

| S.NO | Patho no | HPE Diagnosis | MIB INDEX |
|---|---|---|---|
| 1. | 2484/11 | Astrocytoma – grade - I | <1 % |
| 2. | 272/11 | Astrocytoma – grade -II | 2 % |
| 3. | 2630/11 | Astrocytoma – grade III | 50-60% |
| 4. | 2307B/110 | Astrocytoma – grade - IV | 80% |
| 5. | 4535/11 | Gliosarcoma | 60% |
| 6. | 4258/10 | Meningioma- grade - I | 0.1% |
| 7. | 1561/11 | Meningioma- grade - II | 8-10 % |
| 8. | 1261/12 | Meningioma- grade- III (Rhabdoid) | 20 % |
| 9. | 217/12 | Oligodendroglioma | 0.5% |
| 10. | 3929/11 | Ganglioglioma | Negative |
| 11. | 1110/11 | Medulloblastoma | 5 % |
| 12. | 2452/10 | Pituitary adenoma | Negative |
| 13. | 1416/11 | Hemangioblastoma | <1 % |
| 14. | 390/12 | Schwannoma | < 0.1% |
| 15. | 1952/10 | Ependymoma | 1% |

## CHART -13

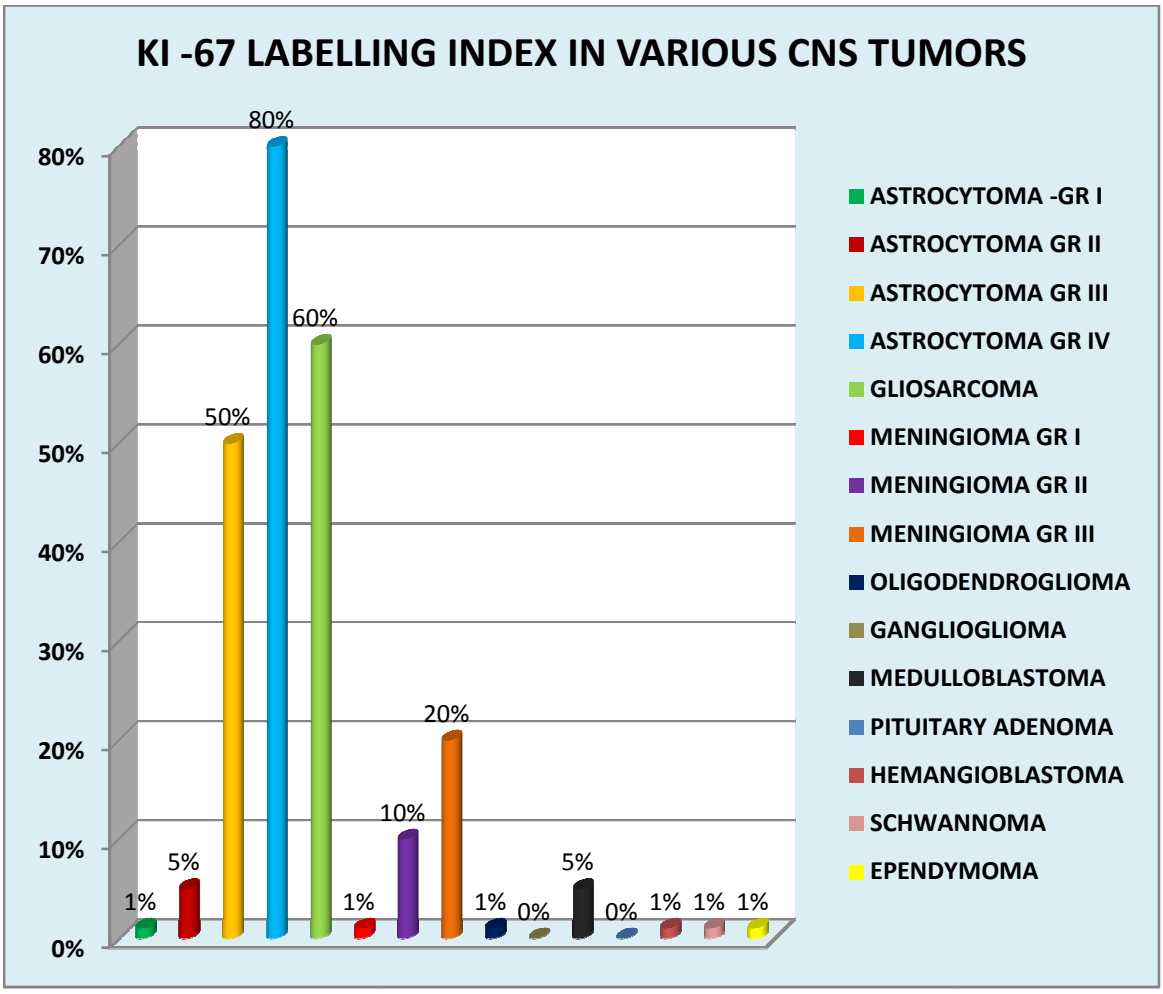

KI -67 LABELLING INDEX IN VARIOUS CNS TUMORS
80%
70%
60%
50%
40%
30%
20%
10%
0%
1%
5%
50%
80%
60%
1%
10%
20%
1%
0%
5%
0%
1%
1%
1%
ASTROCYTOMA -GR I
ASTROCYTOMA GR II
ASTROCYTOMA GR III
ASTROCYTOMA GR IV
GLIOSARCOMA
MENINGIOMA GR I
MENINGIOMA GR II
MENINGIOMA GR III
OLIGODENDROGLIOMA
GANGLIOGLIOMA
MEDULLOBLASTOMA
PITUITARY ADENOMA
HEMANGIOBLASTOMA
SCHWANNOMA
EPENDYMOMA

Table 16 (chart- 13) shows the expression of Ki -67 in various CNS neoplasms in this study. Grade I and II astrocytomas showed a very low expression of the antigen (<1 % and 2% respectively) ( fig- 21,22), indicating the low mitotic activity. Whereas the grade III and grade IV astrocytomas and gliosarcoma showed more than 50 % positivity.(fig – 23,24,25) Similarly in meningiomas as the grade increased a significant increase in the Ki 67 expression was observed with highest expression in rhabdoid meningioma -20% ( grade III ) (fig- 28). There was very minimal expression of the antigen in grade I/II meningioma of <0.1 %.(fig 26,27 ). Oligodendroglioma showed a labelling index of 0.5% (fig 29). Medulloblastoma being a grade IV tumor showed an expression of 5 % (fig 30). Other low grade tumors like ependymoma (1%) (fig 35), hemangioblastoma (< 1% ) (fig 34) and schwannoma (<0.1%) (fig31) showed very little expression of Ki 67 indicating very low mitotic activity and less aggressive nature of these tumors. Ki 67 labelling index was negative in ganglioglioma and in pituitary adenoma.

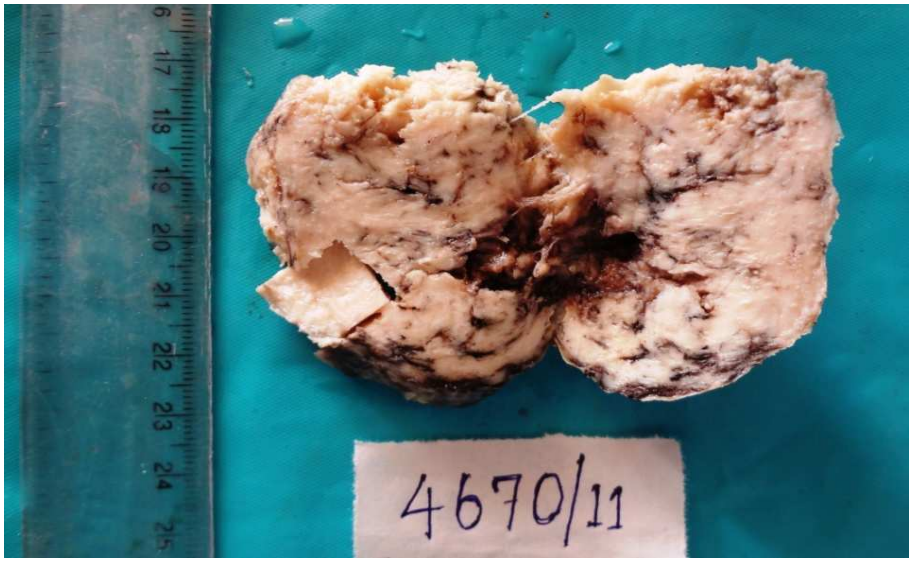



**Figure – 1 Gross specimen of TRANSITIONAL MENINGIOMA showing a fairly circumscribed grey white fibrous mass with focal areas of haemorhage**

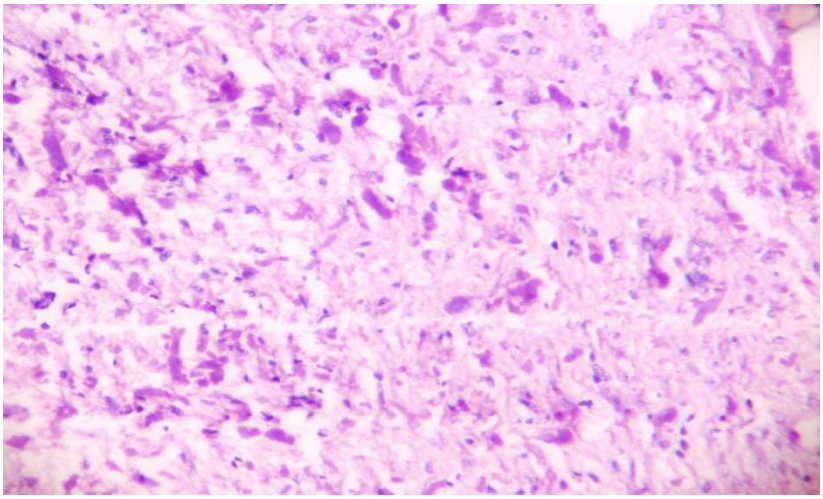


**Figure- 2 PILOCYTIC ASTROCYTOMA GRADE –I numerous Rosenthal fibres lie among a delicate network of hair like cytoplasmic processes H&E**

**(40 X)**

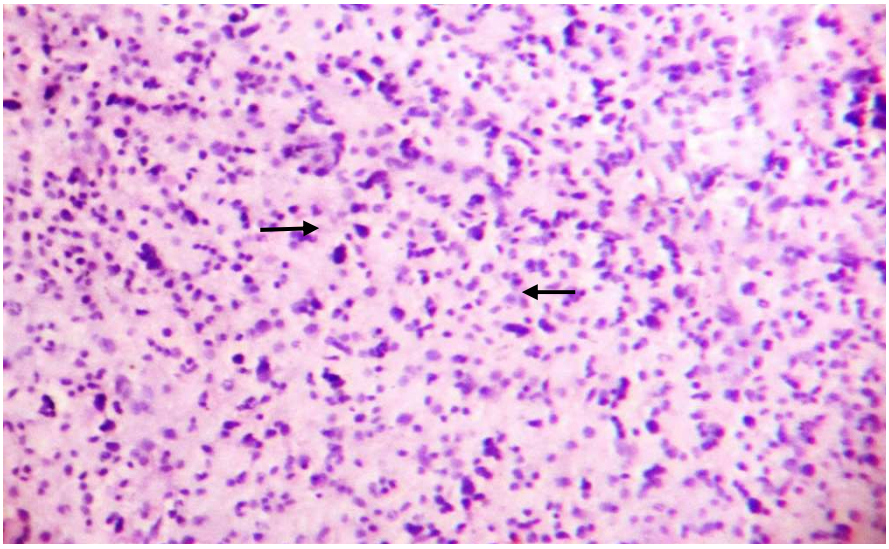


**Figure- 3 ASTROCYTOMA GRADE –II. Cellular tumor containing large and hyperchromatic nuclei with irregular nuclear contours. H&E (40 X)**

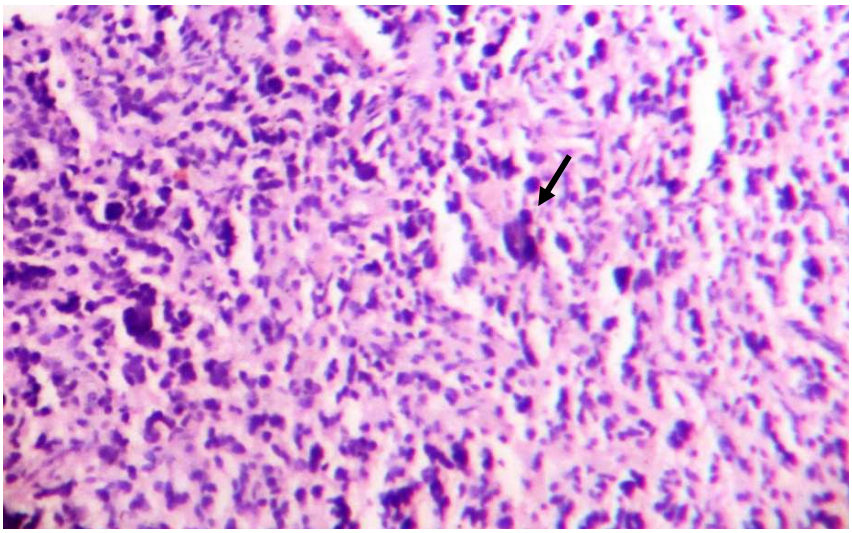


**Figure- 4 ASTROCYTOMA GRADE –III Cellular tumor exhibiting diffuse anaplasia,nuclear pleomorphism and increased mitosis H& E (40 X)**

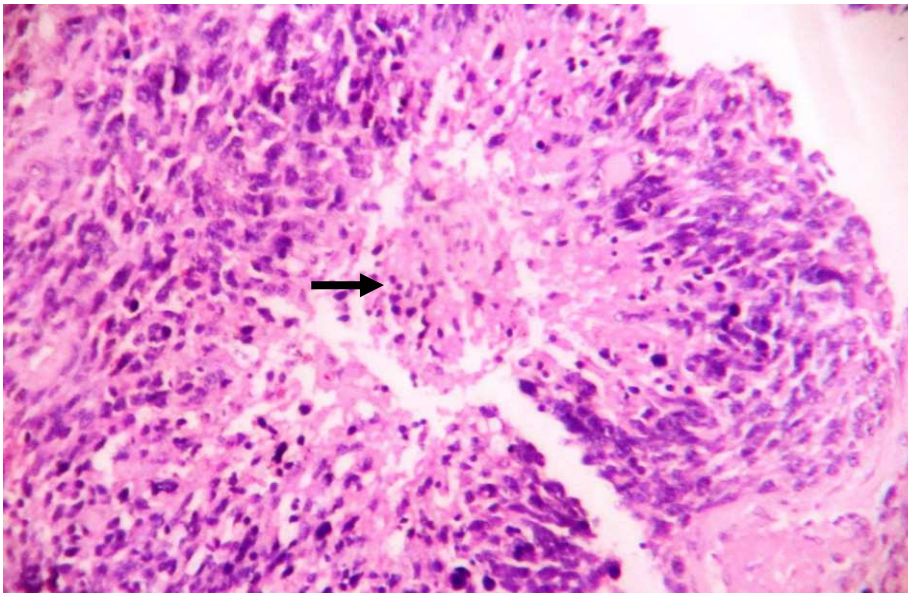


**Figure -5 ASTROCYTOMA GRADE –IV (GBM) - pseudopallisading necrosis with a rim of radially oriented cells around a hypocellular center with scattered pyknotic nuclear debris. H&E (40 X)**

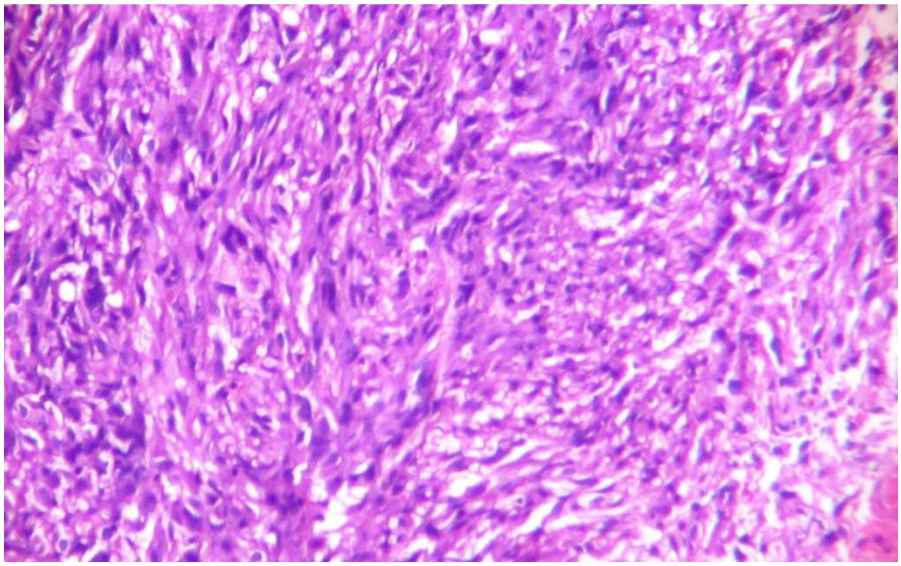


**Figure -6 GLIOSARCOMA-biphasic tumor with spindle cells sarcomatous element and scattered islands of residual fibrillar pink astrocytoma fascicles of spindle cells with mitosis H& E (40 X )**

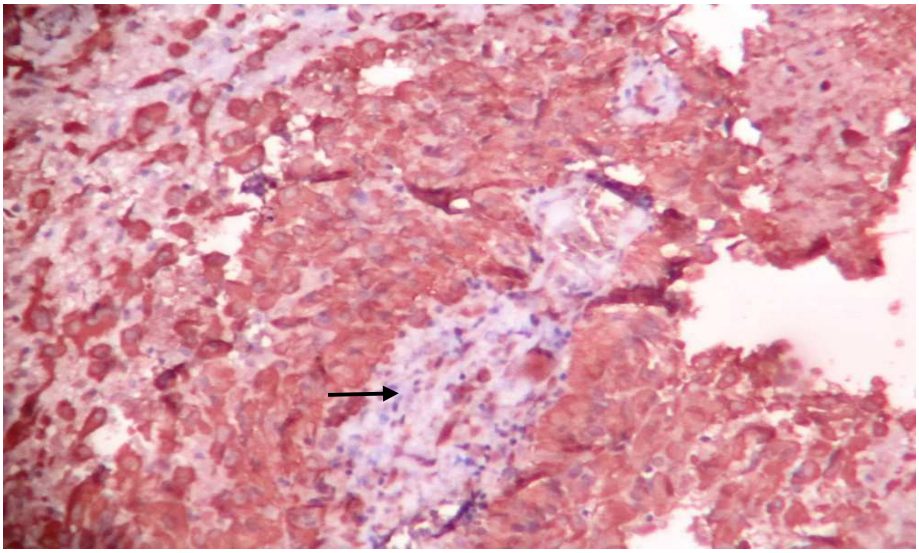


**Figure -7 GLIOSARCOMA – GFAP immunostaining- showing cytoplasmic positivity in the glial cells and negative staining in the non glial area.**

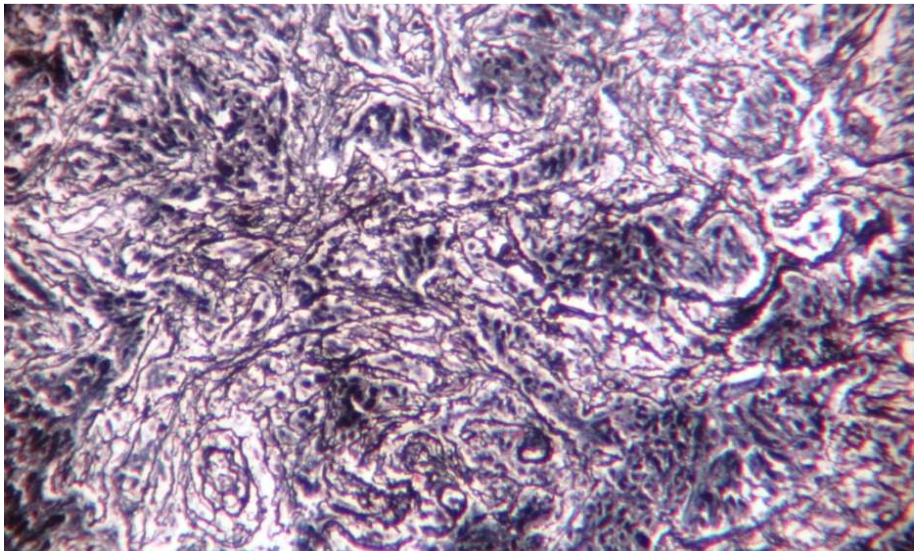


**Figure 8- GLIOSARCOMA– Reticulin deposition is seen around the individual and small nests of tumor cells. Reticulin stain (40 X)**

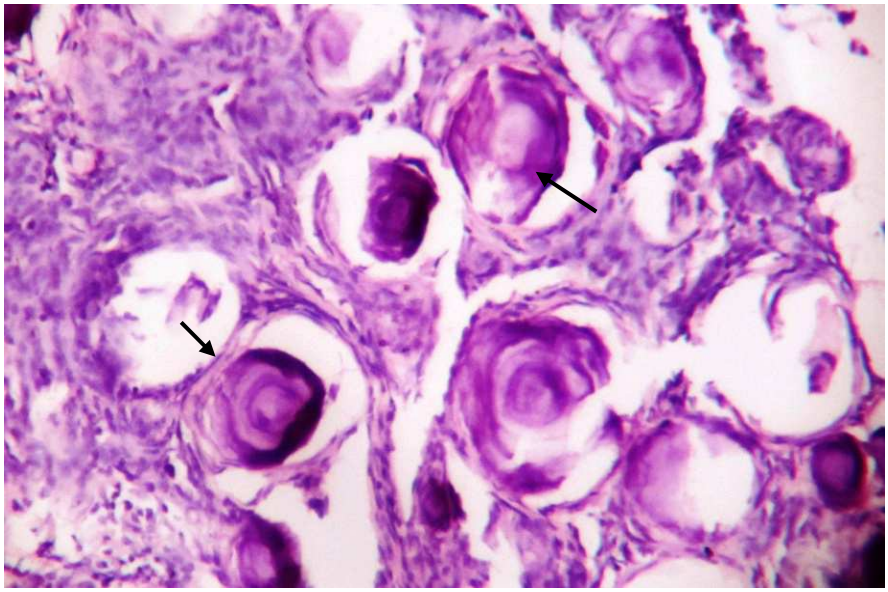


**Figure -9 PSAMMOMATOUS MENINGIOMA (GRADE – I) numerous whorls of meningothelial cells and formed lamellated spheres of Psammoma bodies H& E (10 X)**

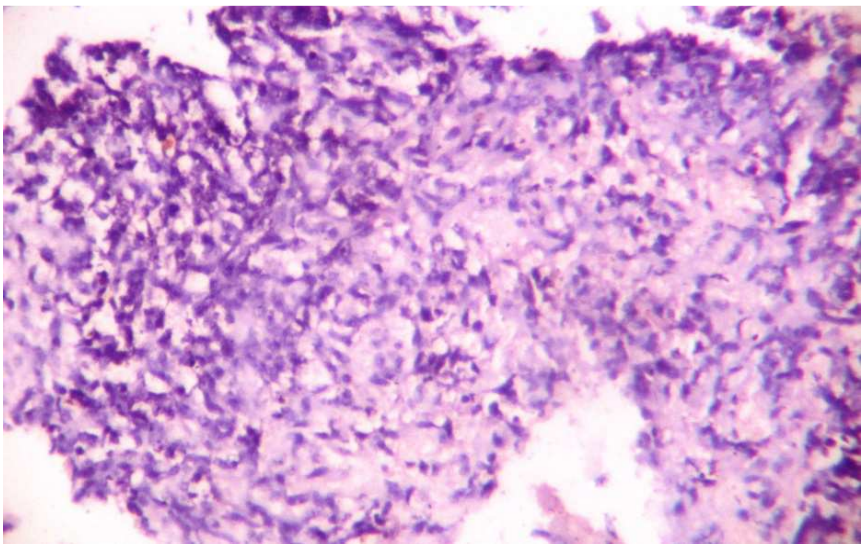


**Figure -10 GRADE II MENINGIOMA showing loss of architecture, sheeting pattern and increased mitotic activity. H& E (10 X )**

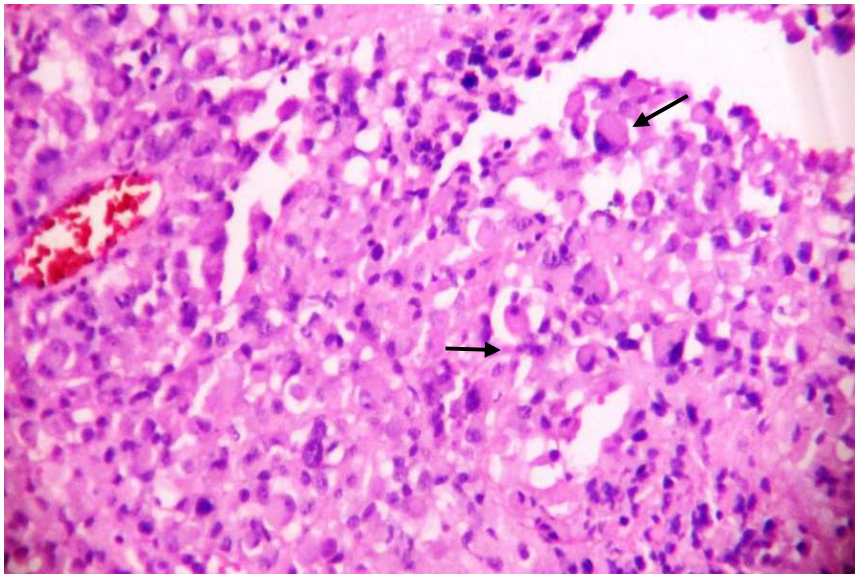


**Figure 11 RHABDOID MENINGIOMA GRADE -III - showing rhabdoid cells with eccentric, eosinophilic, spherical,cytoplasmic inclusion compressing the nucleus against the plasma membrane- H&E (10 X)**

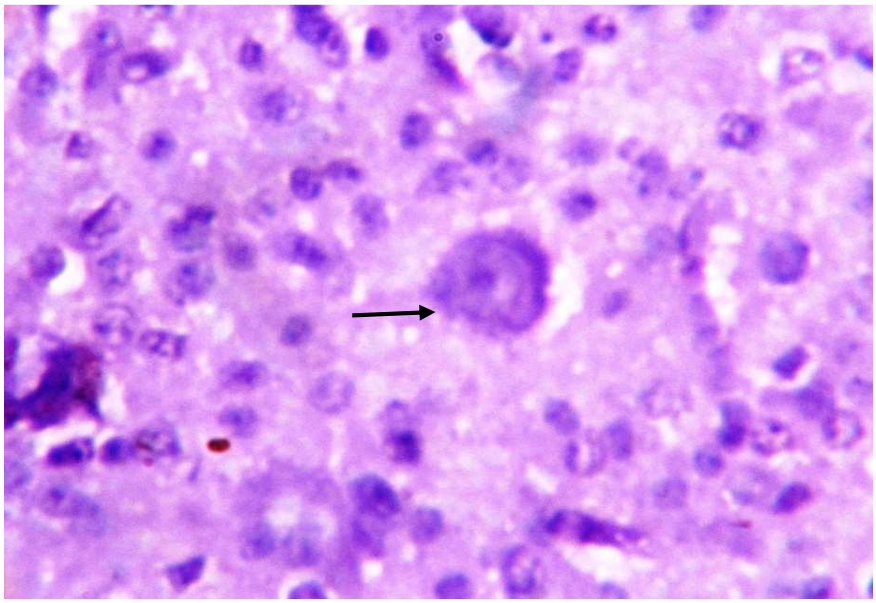


**Figure – 12 GANGLIOGLIOMA- Biphasic tumor with a neoplastic ganglion cell surrounded by glial cells- H& E (40 X)**

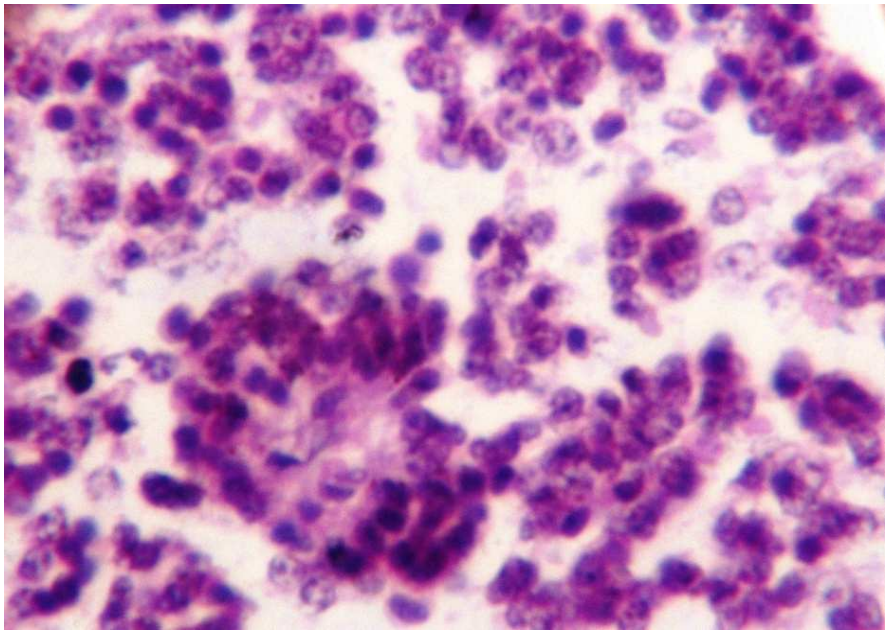


**Figure -13 PITUITARY ADENOMA- uniform small round cells with scanty eosinophilic cytoplasm H&E (40 X)**

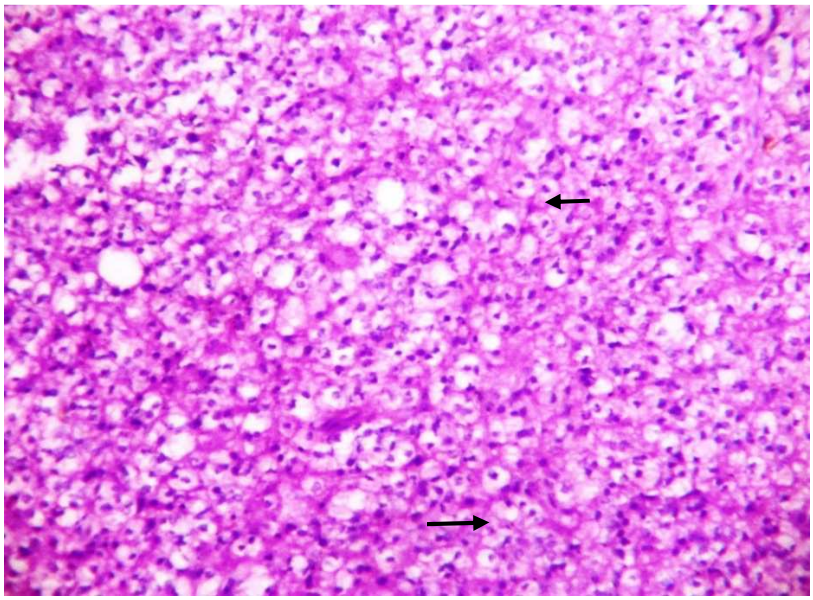


**Figure -14 OLIGODENDROGLIOMA- composed of uniform, round, regular nuclei surrounded by a clear cytoplasmic halo H&E (10 X )**

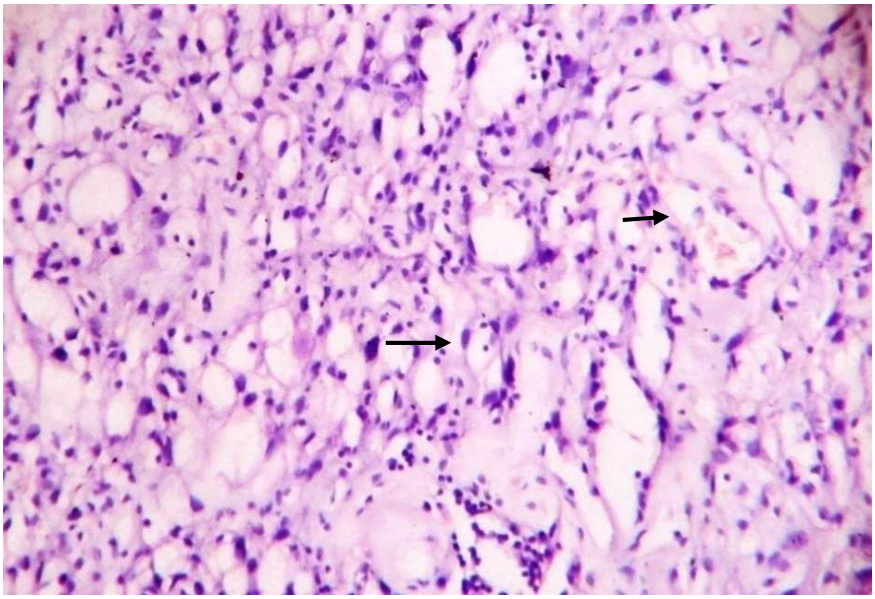


**Figure -15 HEMANGIOBLASTOMA- showing dense capillary meshwork and finely interspersed vacuolated stromal cells H& E (10 X)**

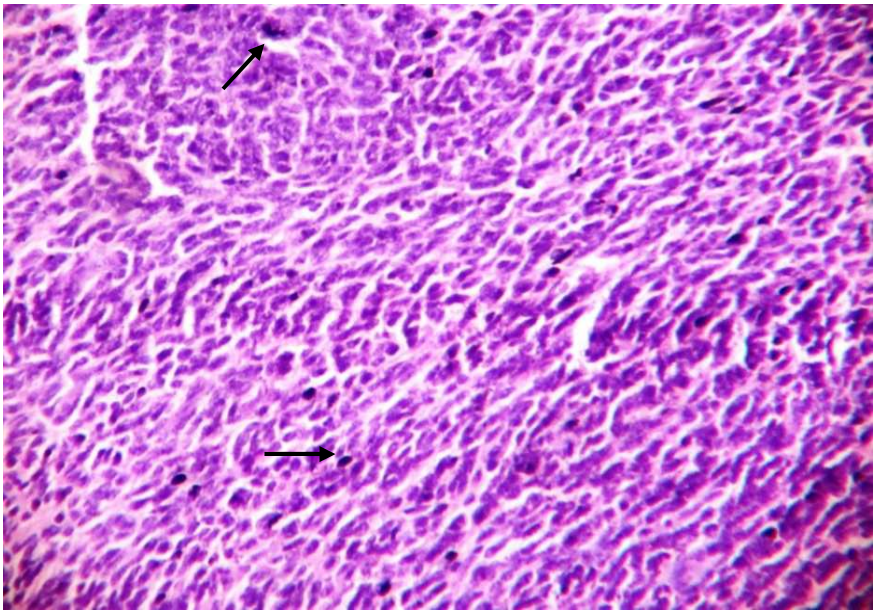


**Figure – 16 MEDULLOBLASTOMA – poorly differentiated sheets of cells with hyperchromatic nuclei and minimal cytoplasm. Numerous mitotic figures are seen**

**H& E (10 X)**

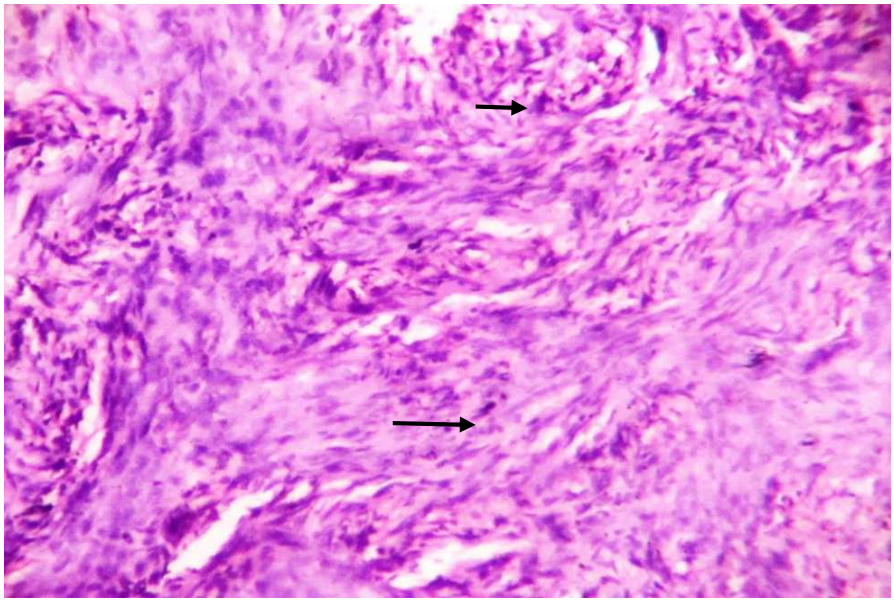


**Figure -17 MPNST –long fascicles of malignant spindle cells with hyperchromatic, atypical nuclei and increased mitotis H& E (10 X)**

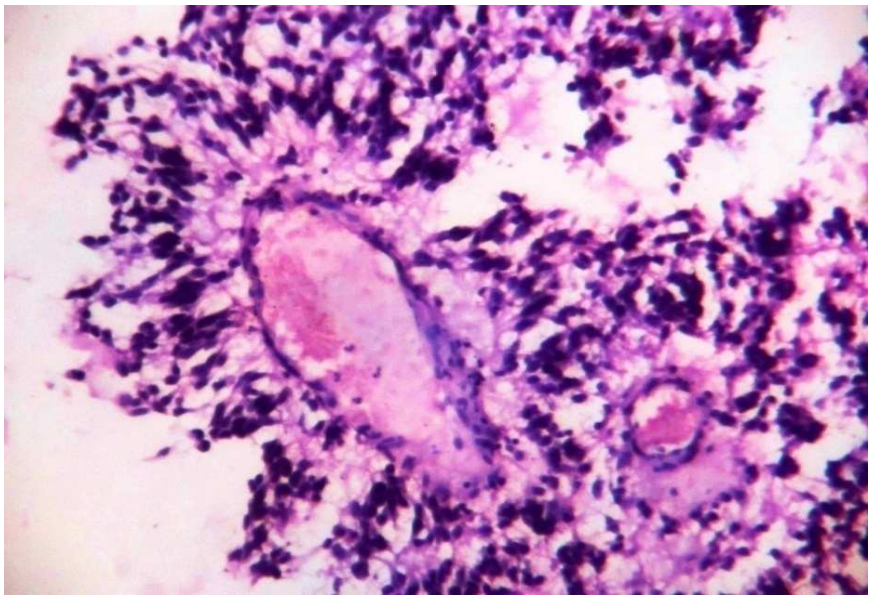


**Figure -18 EPENDYMOMA- perivascular pseudorosette consisting of ependymal tumor cells oriented around a central blood vessel with long fibrillar processes that extend radially towards the vessel H & E (10 X)**

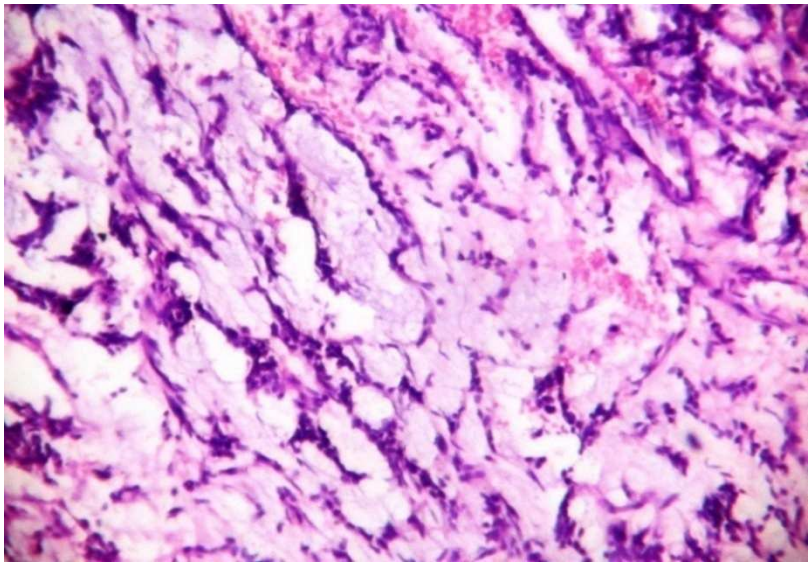


**Figure -19 MYXOPAPILLARY EPENDYMOMA –microcystic appearance with pools of mucinous material among a monomorphic population of fibrillar glial cells H & E (40 X)**

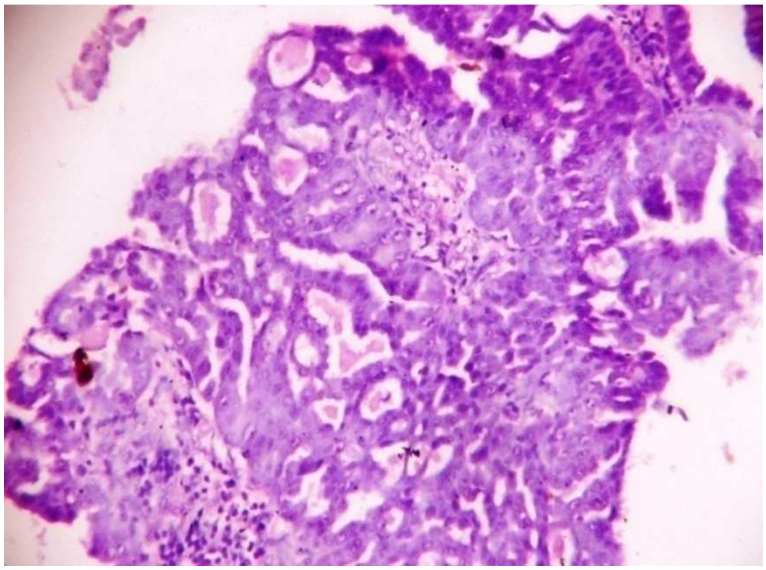


**Figure -20 METASTATIC ADENOCARCINOMATOUS DEPOSIT.Gland spaces lined by malignant epithelial cells H & E (10 X)**

# KI- 67 IMMUNOPROFILE OF CNS TUMORS

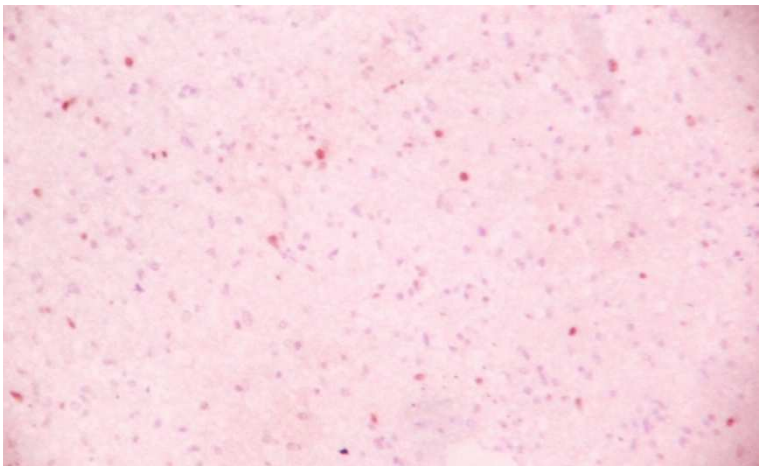


**Figure -21 ASTROCYTOMA GRADE –I, Ki-67 labelling index- <1%, (10 X)**

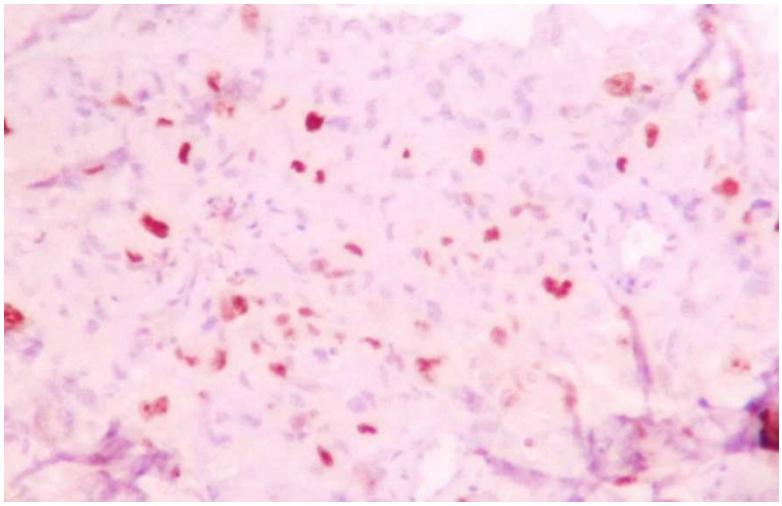


**Figure -22 ASTROCYTOMA GRADE II- Ki67 labelling index - 5% (10 X)**

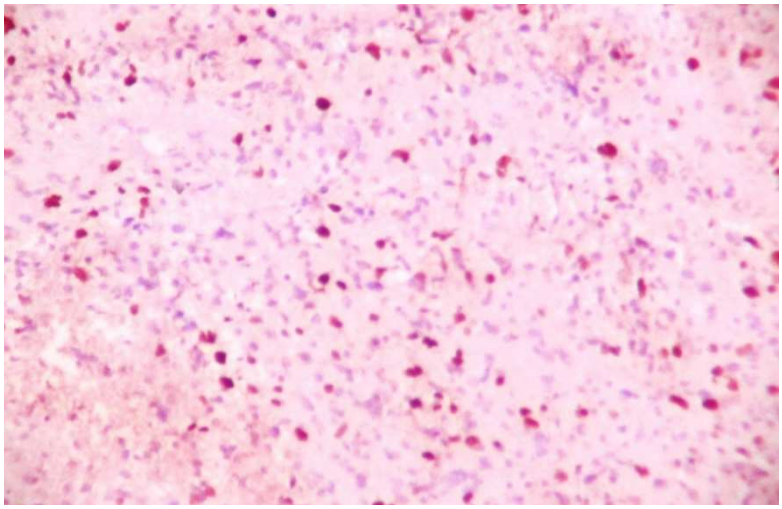


**Figure -23 ASTROCYTOMA GRADE III Ki -67 labelling index – 50 %**

**(10 X)**

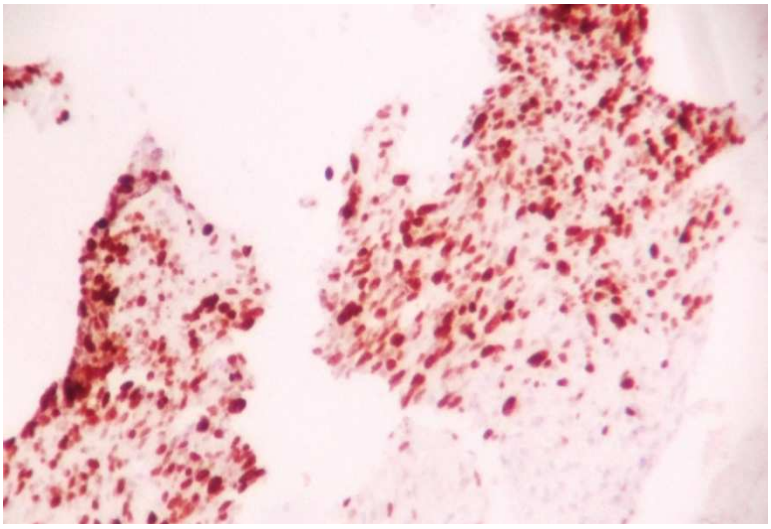


**Figure – 24 ASTROCYTOMA GRADE IV, Ki-67 labelling index - > 80 %**
**(10 X)**

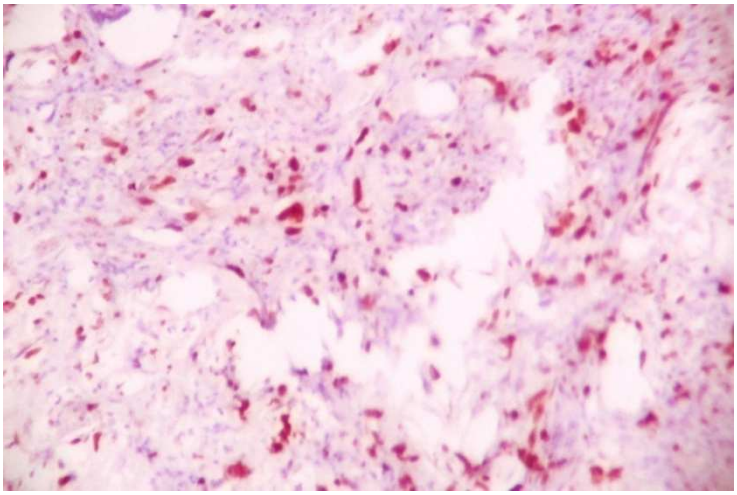


**Figure -25 GLIOSARCOMA , Ki-67 labelling index > 60%, (10 X)**

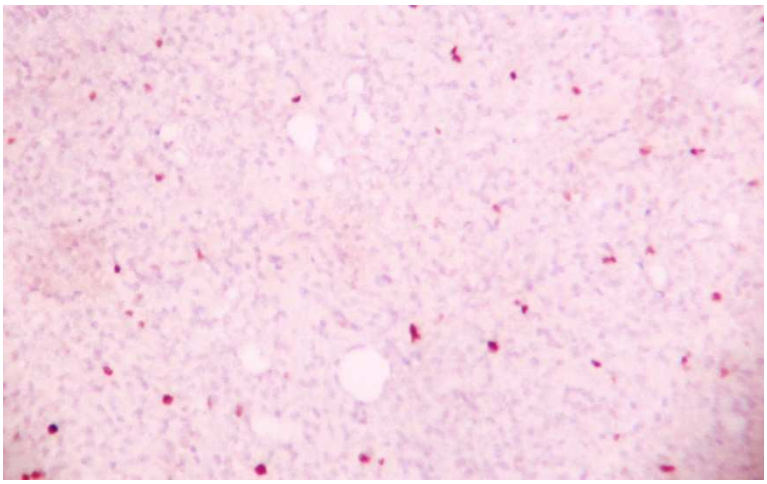


**Figure -26 MENINGIOMA GRADE I , Ki -67 labelling index 1 % (40 X)**

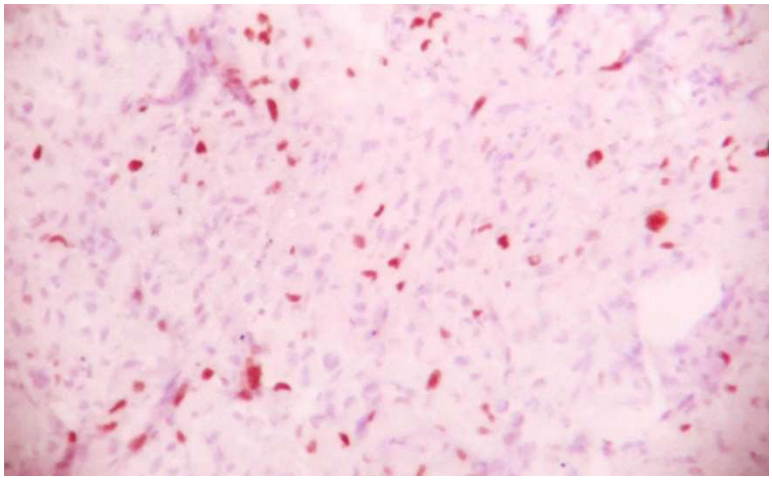


**Figure – 27 MENINGIOMA GRADE II, Ki-67 labelling index 10 % (10 X)**

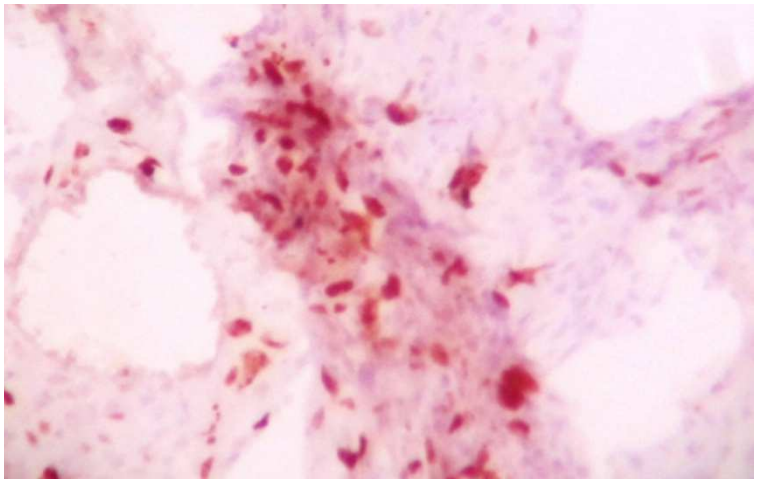


**Figure -28 MENINGIOMA GRADE III, Ki- 67 labelling index 20 %**

**(10 X)**

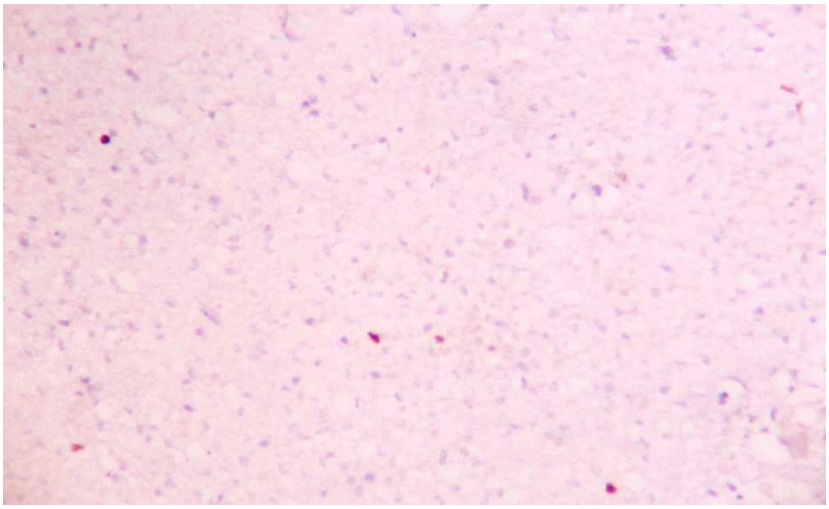


**Figure -29 OLIOGODENDROGLIOMA Ki -67 labelling index 0.5 %**

**(10 X)**

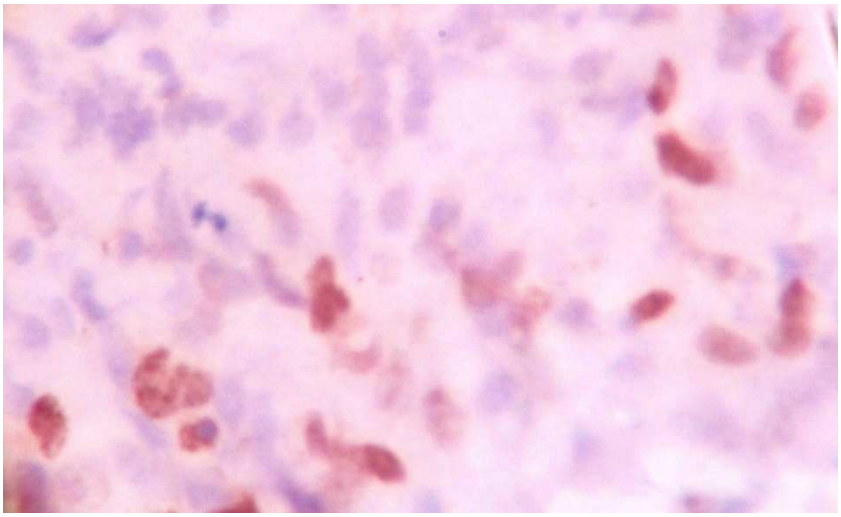


**Figure -30 MEDULLOBLASTOMA Ki-67 labelling index -5 % (40 x)**

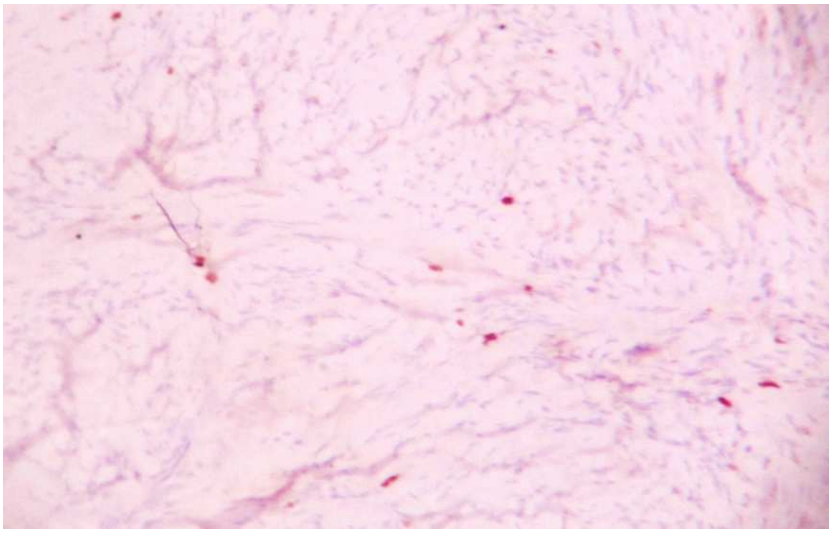


**Figure -31 SCHWANNOMA Ki-67 labelling index - <1 % (10 X)**

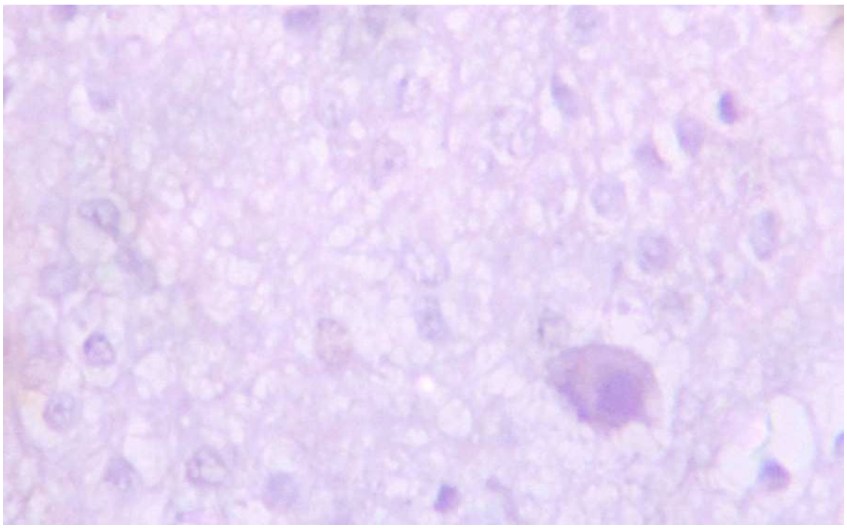


**Figure -32 GANGLIOGLIOMA showing negative Ki-67 immunoprofile (10 X )**

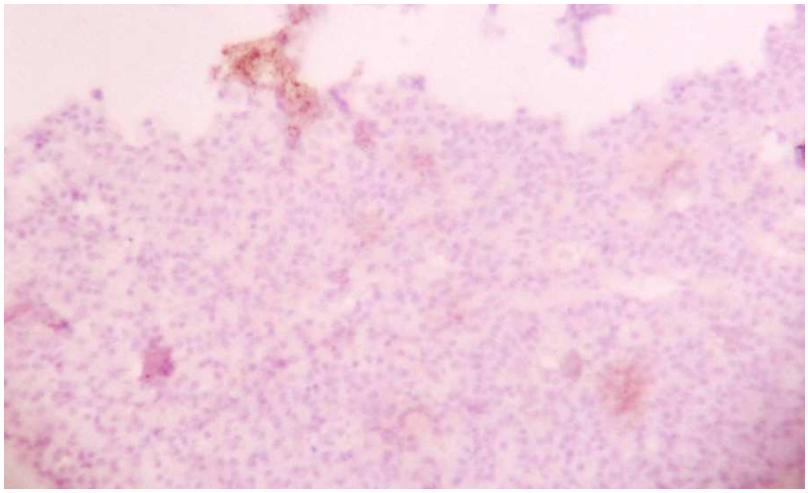


**Figure -33 PITUITARY ADENOMA showing negative Ki-67 immunoprofile (10 X )**

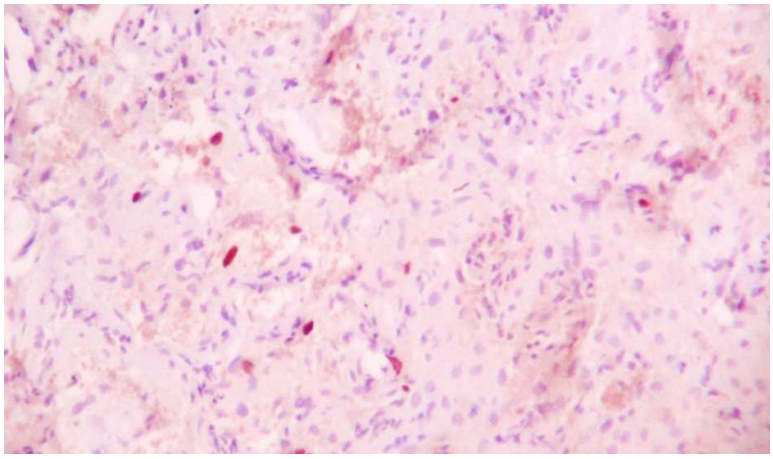


**Figure – 34 HEMANGIOBLASTOMA Ki-67 labelling index 1% (10 X)**

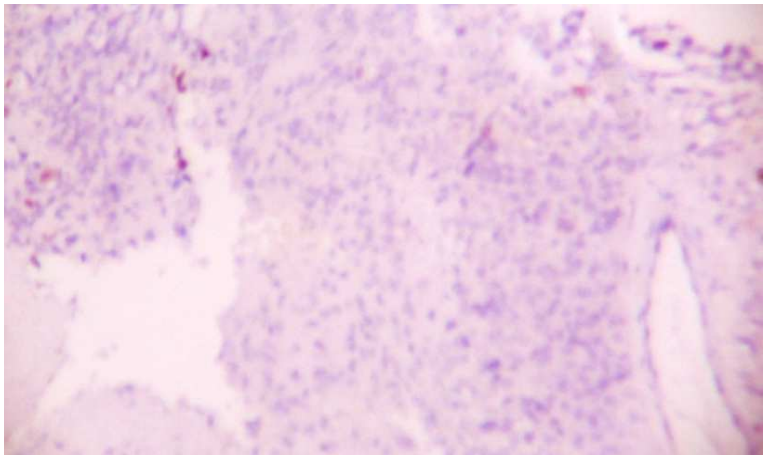


**Figure -35 EPENDYMOMA , Ki-67 labelling index <1% (10 X)**

# *DISCUSSION*

## DISCUSSION:

The central nervous system tumors are the most widely classified of all the other tumors of major systems of the body, with around 86 major tumor types apart from their variants. The CNS tumors are always a cause of concern among histopathologists due to its wide variation in the morphology and also the difficulties faced in grading these tumors accurately.

In the present study about 100 CNS tumors, reported in the department of Pathology at TMC, were analysed. The incidence of CNS neoplasm during the time period between Jan 2010- May 2012 were found to be 8.19%.

According to the data of the CBTRUS ( Central Brain Tumor Registry of the United States) [12] the overall rate of occurrence of CNS tumors is about 19.34 per 100,000 person years. According to Chang Hyun et al[16] it was 11.69 per 100,000 person years.

There are many well established studies like that of Chang et al[16] to prove that there are great variations in the occurrences of various CNS neoplasms according to the age gender, ethnicity and geography. In this study too there were a wide variation in the distribution of tumors according to age, sex and location. Most commonly the CNS tumors occurred in the age group of 31 -40 years (24%) followed by 41-50 years(20%). CNS neoplasms least commonly occurred in the 70- 80 years age group (2%) in our study. This was

in accordance to the study of N.B.Andrew et al[74] where the mean age of occurrence was 39 years. Studies conducted by A.Das et al[1], and Aryal G[37] and Manoharan et al[75] showed an increase in the incidence of CNS tumors as the age increases.

N.Manoharan et al[75] showed that the CNS tumors were more common in the male population (65%) than in the females in Delhi . Similarly there was a male predominance (54%) in our study. This was against the CBTRUS[14] data (female 57%) and the study of Chang Hyun[16] (58 % in females). This discrepancy could have been because of more number of meningiomas that predominated in the females in these studies.

Sites of CNS tumors are significant in many aspects. Arrie Perry[85] states that because the central nervous system is a complex structure with various subdivisions that have differing functions and different susceptibility to particular neoplasms, it is not only important to designate the overall site of the tumor like brain, spinal cord, nerves but also to specify the region of the brain and meninges like frontal, temporal, parietal. Such designations are of great value for future studies as the behaviour of the CNS tumors varies by site. Eg there is different prognosis of a frontal convexity meningioma in comparison to one growing along the sphenoid wing. Moreover according to Jill et al[104] relative survival rates (%) did differ by primary site, with tumors in the cerebrum, parietal lobe, occipital lobe and overlapping lesions of the brain

having the poorest survival, less than 20 % at 5 years. The commonest site of CNS neoplasm in our study was in the frontal lobe (25%) followed by the parietal lobe (23%). This was in accordance with the studies of N.BAndrew et al[74] and Chang et al[16]. Whereas Intisar et al[44] showed a predominance in the parietal lobe.

According to Douglas Miller[24], Pathologist could likely construct elaborate grading schemes for tumors in general and astrocytomas in particular, with any number of different categories. These might be reproducible, teachable to others, and they might be even based on objective observations on which multiple observers could reliably agree. The point of tumor grading however is to provide a statistical observation derived from populations of tumor patients but applied to an individual case presently under observation in order to guide therapeutic decisions and give a sense of the survival probability for the patient represented by the case.

Grading of the CNS tumors in this study was done according to the WHO 2007 criteria[51]. The grading was based on the cellularity, mitotic count, microvascular proliferations, necrosis. In our study it was seen that the grade I tumors were more common (42%) with lesser occurrence of grade IV tumors (27%). Also it was noted that grade I and grade II tumors occurred more commonly in the third decade in accordance with the study of Peter et al who

showed a similar occurrence in grade II tumors. Grade IV tumors had bimodal peak of occurrence in the second and in the fourth decade.

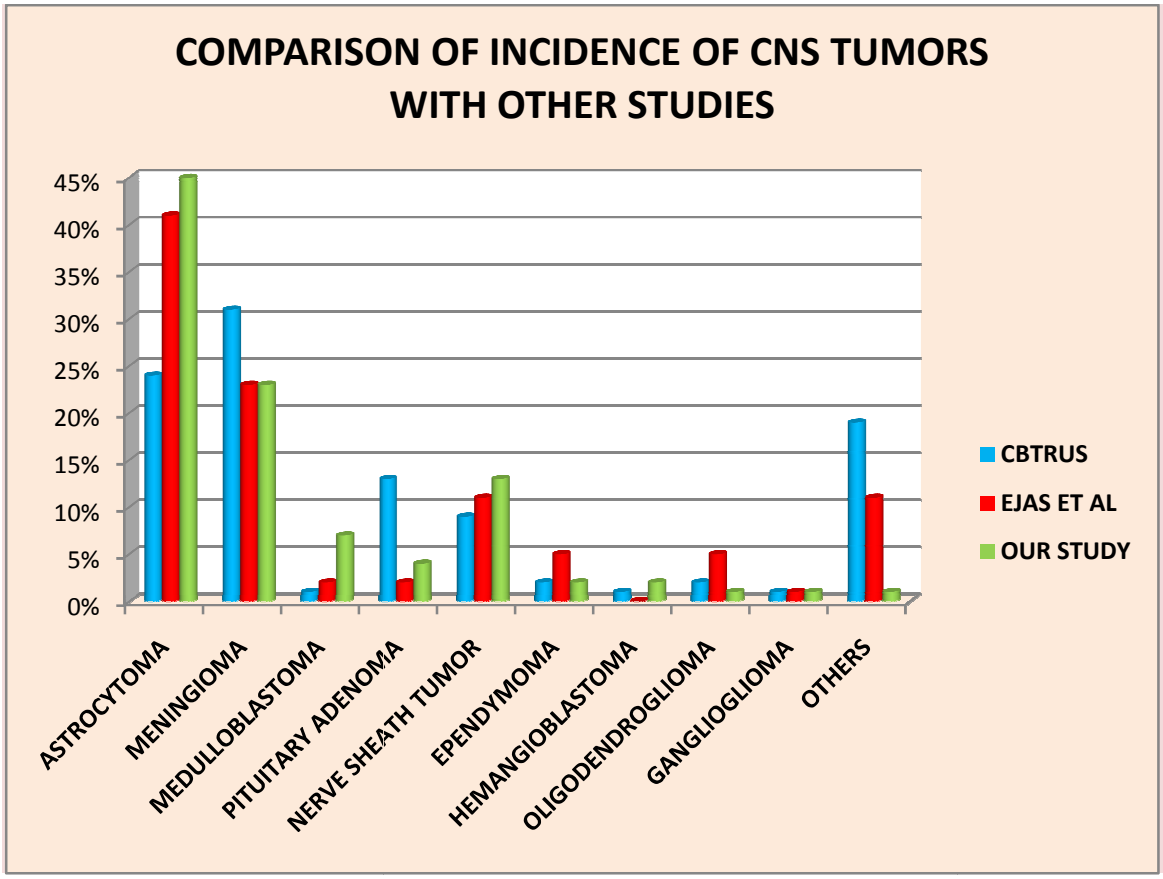
Sex wise incidence showed that the females (53%) outnumbered the males (33%) in grade I tumors that was because of many cases of meningiomas in our study that usually have a predilection for females, whereas males predominated in all other grades of CNS neoplasms.

A comparative analysis of the incidence of various CNS tumors at different geographic locations by various studies[14,62,37,11] is shown in the following table (chart- 14)

**Table – 17 Comparison of incidence of CNS tumors in various studies**

| Tumor | CBTRUS | Ejas et al | Aryal.G | Bushra Ayaz | Our study |
|---|---|---|---|---|---|
| Astrocytoma | 23.7 % | 41% | 38.6% | 48% | 45% |
| Meningioma | 31.4 % | 23% | 14% | 18% | 23% |
| Medulloblastoma | 1% | 2.4% | 3.5% | 4% | 7% |
| Pituitary adenoma | 13.1% | 2% | 5.2% | - | 4% |
| Nerve sheath tumors | 8.6% | 11% | 8.7% | 1% | 13% |
| Ependymoma | 1.8% | 4.8% | 1.8% | 6% | 2% |
| Hemangioblastoma | 0.8% | - | - | 4% | 2% |
| Oligodendroglioma | 2% | 4.8% | - | 8% | 1% |
| Ganglioglioma | 0.2% | - | - | - | 1% |
| Others | 19.2% | 11% | 28.2% | 11% | 2% |

## CHART -14


COMPARISON OF INCIDENCE OF CNS TUMORS WITH OTHER STUDIES
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
ASTROCYTOMA
MENINGIOMA
MEDULLOBLASTOMA
PITUITARY ADENOMA
NERVE SHEATH TUMOR
EPENDYMOMA
HEMANGIOBLASTOMA
OLIGODENDROGLIOMA
GANGLIOGLIOMA
OTHERS
CBTRUS
EJAS ET AL
OUR STUDY

The distribution of various CNS tumors in our study showed that astrocytomas were the top on the list constituting about 43 % followed by meningiomas 23%, which is in accordance with other studies of M. Ejas et al[62], Aryal G[32] and Bushra et al[11]. According to CBTRUS[14], meningiomas ranks the first followed by astrocytomas. Nerve sheath tumors occupies the third place in the studies by M Ejas[62] and the present studies.(chart-14)

Incidence of glial tumors in various institutions in India[76] in comparison with our study is shown below

**Table – 18**

**Incidence of glial tumors in various institutions in India**

| Study | Astrocytoma | Glioblastoma | Medulloblastoma | Oligodendroglioma | Ependymoma |
|---|---|---|---|---|---|
| Tata Memorial Hospital, Mumbai | 46.3% | 21.5% | 11.1 | 6.3% | 6.8% |
| Kidwai Memorial Institute of oncology Bangalore | 41.1% | 22.95% | 11.2% | 9.6% | 1.92% |
| Cancer institute,Adyar | 39% | 29.05% | 5.9% | 4.4% | 3.4% |
| Regional cancer institute,Trivandrum | 41.35% | 13.3% | 12.7% | 3.35% | 2.1% |
| Assam Medical college, Dissugarh | 46.75% | 7.1% | 8.1% | 9.1% | 7.1% |
| Present study | 25% | 20% | 7% | 1% | 2% |

The above tables show that astrocytoma is the most common glioma in our study consistent with other studies in various institutions. Astrocytomas are primary CNS tumors that was previously classified in to three histological types: Fibrillary astrocytoma (WHO grade I and II), Anaplastic astrocytoma ( WHO grade III) and Glioblastoma (WHO grade IV). The reason for classification and grading of astrocytomas is to help in chosing the right management protocol.

Astrocytomas are further graded by the WHO based on the nuclear atypia, mitosis, microvascular proliferations and necrosis ( AMEN criteria)[51] into four grades. The following are the incidence of various grade of astrocytomas in different studies

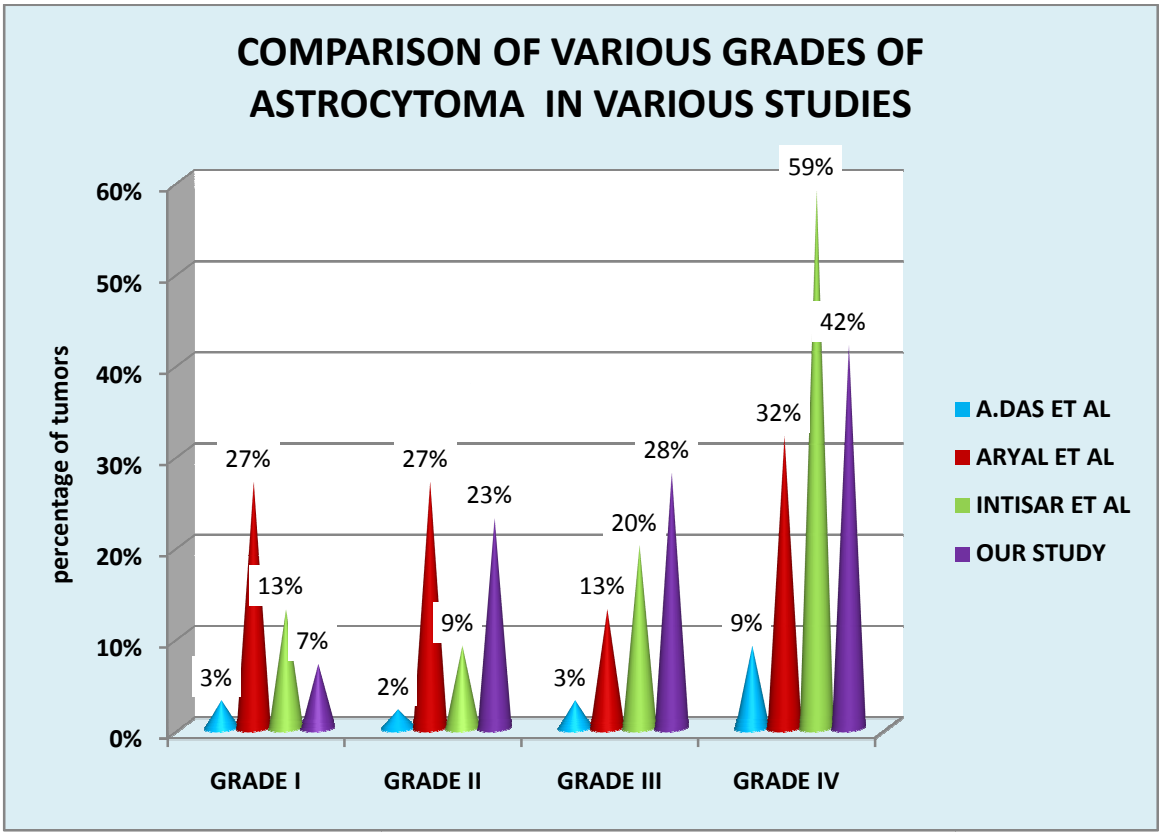
**Table – 19**

**Comparison of grades of astrocytomas with other studies**

| Studies | Grade I | Grade II | Grade III | Grade IV |
|---|---|---|---|---|
| A.Das et al | 3.3% | 2.4% | 3.3% | 9.3% |
| Aryal | 27.3% | 27.3% | 13.6% | 31.8% |
| Intisar et al | 12.5% | 8.9% | 19.6% | 58.9% |
| Busra Ajas et al | 4% | 11% | 10% | 23% |
| Our study | 6.9% | 23.25% | 27.96% | 41.86% |

The above table 19 (chart 15)shows that grade IV astrocytomas is the commonest grade and grade I astrocytomas shows the least occurrence in majority of the studies ( A.Das et al, Aryal G, A and Intisar et al)[1,37,44] and it is the same in our study also. According to the studies of P Kleihaus et al[53] . Grade

## CHART- 15


COMPARISON OF VARIOUS GRADES OF ASTROCYTOMA IN VARIOUS STUDIES
percentage of tumors
60%
50%
40%
30%
20%
10%
0%
3%
27%
13%
7%
2%
27%
9%
23%
3%
13%
20%
28%
9%
32%
59%
42%
GRADE I
GRADE II
GRADE III
GRADE IV
A.DAS ET AL
ARYAL ET AL
INTISAR ET AL
OUR STUDY

I and II are common in the 30-40 yrs age group which is consistent in our study also, whereas the grade IV astrocytomas occurred in a much older age group 40-50 years which is consistent with the study of Zulch KJ et al who gave a peak incidence between 45- 70 years.(chart- 15

Regarding the sex wise incidence of various grades of astrocytomas our study showed an increase in incidence in males (67%) in all the grades than in the females (33%). This is in accordance with the study of A.Das[1] and Intisar et al [44]who also showed an increase in incidence in the males.

Meningiomas are relatively common intracranial neoplasm in India. The majority occur in the elderly age group. Meningiomas are generally benign neoplasms and although they exhibit a variety of well described histologic patterns, none of these have any bearing on the prognosis. Instead the prognosis is influenced by the completeness of excision and aggressive nature with increases mitosis, necrosis and prominent cytological atypia.[93]

Meningiomas constituted the second largest group of CNS tumors in our study (23%). This was comparable to the study of NB Andrew et al[74](19.2%), Ejas et al[62] (23%). All the cases were graded on the basis of the WHO criteria which included cellularity, pattern, mitosis and necrosis. Out of the 23 cases, grade I tumors constituted about 19 cases – 82.6%) and this is similar to the data of Sameh et al[102] (86.5%) and Sasidhar et al[103] ( 90%). One case of rhabdoid meningioma (grade III) was observed in our study. Only one case of atypical

meningioma ( grade II) was observed constituting about 4.3%. Jaas kelainen et al[45] also showed an incidence of 1-2.8 % for grade II meningiomas.

According to the study of Paul Kliehaus et al[52] and Mahmood et al [63] meningiomas are common in the sixth and the seventh decade. In contrast our study showed an increase in incidence in the third and the fourth decade (26.085 and 21.73%). An increased incidence was noted in the females(87%) which correlated with majority of studies done worldwide. According to Perry A et al[85] atypical and anaplastic meningiomas may show a conspicuous male predominance, but this fact did not correlate in our study as both the cases of grade II and grade III meningiomas occurred in females. Another interesting fact regarding the sex incidence is that according to Sheik et al[107], Hope JK et al[40] and Erdincler P et al[31] childhood meningiomas are more common in males and spinal cord meningiomas were more common in females. In our study we have no such incidence of meningiomas in the spinal cord.

The nerve sheath tumor were the next more common tumors in our study. Schwannomas constituted about 9 % and neurofibromas about 8 %. One case of low grade MPNST was reported from the spinal cord. Intisar et al[44] showed an incidence of 3.9% for schwannomas and 2.4 % for neurofibromas. The mean age of occurrence was about 35 years for all nerve sheath tumors. Also there was an overall male predominance with the male female ratio of 1.3:1,which correlated with Intisar et al (1.5:1). All the neurofibromas occurred in the spine

8%) and most of the schwannomas occurred in the CP angle.many vestibular schwannomas are predominantly Antoni A tissue and relatively hypercellular compared to other locations and lack the nuclear pallisading according to Celli et al [13] According to a recent study in a series of 430 spinal tumors, unlike schwannomas , neurofibromas are uncommon in the cranial and spinal nerves constituting only 6 cases(Engel et al)[30]. We reported one case of MPNST in a 35 years old female in the D1-D3 level of the spine. According to Ducatman BS[26] et al MPNST is a very rare tumor in the spinal cord constituting only about 0.001 % of the reference population. As in our case this tumor is more common in females. Prognosis of MPNST arising primarily from the spine in not good ( Celli et al ). Seppala MT et al[105] in his study has shown that there is a 71 % recurrence rate and metastasis to the lung in 33 % of cases.As per the study of N.B Andrew et al[74] spinal cord tumors constituted to about 13% of CNS tumors and according to Bushra et al[11] it constitutes to 15 %. In our study we have found an incidence of 9% of spinal tumors out of which 7( 78%) were neural tumors and there were one case each of meningioma(11% and myxopapillary ependymoma (11%)

Hemangioblastomas are highly vascular tumors which occupy a special niche in the universe of primary CNS neoplasms they are formed of two principal components, vascular elements and interstitial or stromal cells. The varied ratios of these two elements, the calibre of the vascular channels

(predominantly capillaries) and the degree of lipidization of stromal cells contribute to the histological heterogeneity of hemangioblastomas. Two cases of hemangioblastomas were reported in our study constituting 2% of CNS tumors. This was in accordance with the studies of A.Das[1](2.2%)and Miyagami et al [72] (2.1%). Both the cases occurred in males. Hemangioblastomas are slow growing tumors that commonly occur in the cerebellum and occur in association with Von Hippel –Lindau disease. In our study one case occurred in the cerebellum but other occurred in the parietal lobe. No syndromic association was noted in both cases. Miyagami et al[72] have emphasized that sporadic hemangioblastomas have a good long term prognosis in contrast to the familial VHL disease associated hemangioblastomas.

Oligodendrogliomas constitute about 3 % of the total CNS neoplasms. As per the study by Manoharan et al[75] conducted between 2003 and 2007 with a total of 1989 patients showed an incidence of 5.2% for oligodendrogliomas. We reported one case of oligodendroglioma in a 30 years old male . Most frequent age of occurrence is between 40 and 45 years according to Arie Perry et al[85]. The classical fried egg appearance of the neoplastic cell and the rich branching chicken wire type of blood vessels were observed in our study.

Pituitary adenomas represent about 10-20 % of the intracranial neoplasms[110]. According to Richard A Prayson[93],the histopathological identification of a pituitary adenoma is usually a straightforward even easy

enterprise. So long as the tissue is submitted as from the pituitary and not labelled generically as “brain tumor”. Some adenomas exhibit medium sized cells with a round nuclei in the centre of clear cytoplasm, which may be mistaken for oligodendroglioma and its mimics. Some adenomas have a distinctive perivascular arrangement suggestive of ependymomatous pseudo rosettes. Hence without a proper designation as to site might misdiagnosed and is essential that the pathologist know the location from which the tissue comes. Aryal .G reported that the peak age of occurrence was in 21-40 years age group.

We reported 4 cases of pituitary adenomas. We have observed a wide variation in the age of occurrence, one in a 10 years old male child and the the oldest reported case was in a 70 years old male. The other 2 cases were in women in the third decade . Literature shows that pituitary adenomas are more common in the female population. In our study we had a equal sex incidence. All the cases in our study were macroadenomas > 1 cm diameter.

Ependymomas are tumors that occur in children and young adults and favour the fourth ventricle and spinal cord. In grade II ependymomas there are perivascular pseudorosettes, ependymal canals, rare or no mitosis.Grade III (anaplastic) ependymomas show increased cellularity, brisk mitotic activity, vascular proliferation, endothelial hyperplasia, pseudopallisading necrosis, perivascular rosettes and ependymal canals.[53]

Two cases of ependymomas was included in the study. We reported a case of myxopapillary ependymoma in a 55 years old male. The other case of ependymoma was reported in a 32 years old male. The age group did not tally with most of the literature. A study by Suri et al[111] showed that the mean age of occurrence in his study was 40 years. Arie Perry[85] showed an equal male female ratio. But in our study both were males.

Myxopapillarv ependymomas (grade I) are characterized by cuboidal to elongated tumor cells around vascularized stromal cores in a mucoid matrix. Myxopapillary ependymoma occurred in the spinal cord at the D12 - L1 level. But the site of occurrence of the grade II ependymoma was unusual to be in the frontal lobe. Suri et al[111],showed that there was a 2.16% of occurrence of ependymomas intracranially. Xuetao et al[124] also showed that there can be 2-9 % occurrence of ependymomas intracranially.

One case of ganglioglioma was reported in a 42 years old male constituting 1% of all CNS neoplasms. Wolf et al in his study showed a similar incidence and Arie Perry[85] showed an incidence of < 2% in his study. According to Lay Ken[56] they occur in 2 $^{nd}$- 5$^{th}$ decade and are associated with seizures. They are characterized by the biphasic tumor cell population with neuronal and glial elements. Hirose et al stated that the glial population is the actively dividing component and most cases being grade I or II . Dysmorphic haphazardly arranged ganglion cells dispersed in a glial background was well observed in our study.

Two cases (2%) of metastatic tumors were reported. The tumors occurred secondary to the adenocarcinomas in the colon. Both the cases demonstrated mucin secreting well differentiated glands. One case was in the parietal lobe and the other was in the occipital lobe. Both cases were in the fourth decade and had equal sex incidence. This was in contrast with the study of Paul Kleihaus et al[53] who showed an incidence of 0.03 to 0.04 % with the rate of metastasis higher in the elderly age group.

## CHILDHOOD BRAIN TUMORS

An estimated 2400 children between the ages of 0-19 years are diagnosed with invasive primary central nervous system tumors in the United 100,000 person years (CBTRUS report 2009)[12] . Brain tumors are second only to acute lymbhoblastic leukemia (ALL) in children. The incidence of CNS tumors in children as stated by Smith, Freidlin et al was found to have increased by 35 % between the years 1975-1984. This increase was attributed to the introduction of magnetic resonance imaging (MRI) brain growth occurs rapidly during gestation and peaks around 4 months after birth but continues until 3-4 years thereafter according to Baldwin and Preston –Martin[85] . Hence it is more vulnerable to genotoxic damage and neoplastic transformation than any other organ in the body, due to the relatively longer course of development both in utero and post natal life during which the rapidly dividing cells become susceptible to exposure to potential environment toxins and DNA damage.it

appears that fetal brain is less able to efficiently repair DNA alkylation induced by various mutagenic agents. The blood brain barrier is also not complete in the fetal brain and facilititates free transfer of carcinogens into the vulnerable neural tissue.

Only about 5 % of the CNS tumors are the direct consequence of a specific gene defect. Ron, Modan et al [98] has stated that occurrence of majority of these neoplasms are multifactorial due to the interplay of both genes and the environment. One known environmental cause of brain tumors is ionising radiation and can induce both benign and malignant gliomas or occasionally primitive neuro-ectodermal tumors (PNET)

A total of 13 cases(13%) of pediatric brain tumors occurred in our study. A similar incidence was reported in the study of Manoharan et al [75] (9.3%) and Ayush et al (14.8%). According to the CBTRUS[14] data (2009) about 7 % of the reported brain tumors occurred in children. Pakistan armed forces medical journal[11] reported a 7.4% incidence of childhood brain tumors.

The following were the distribution of various groups of CNS tumors in children in comparison with various studies.

## Table- 20

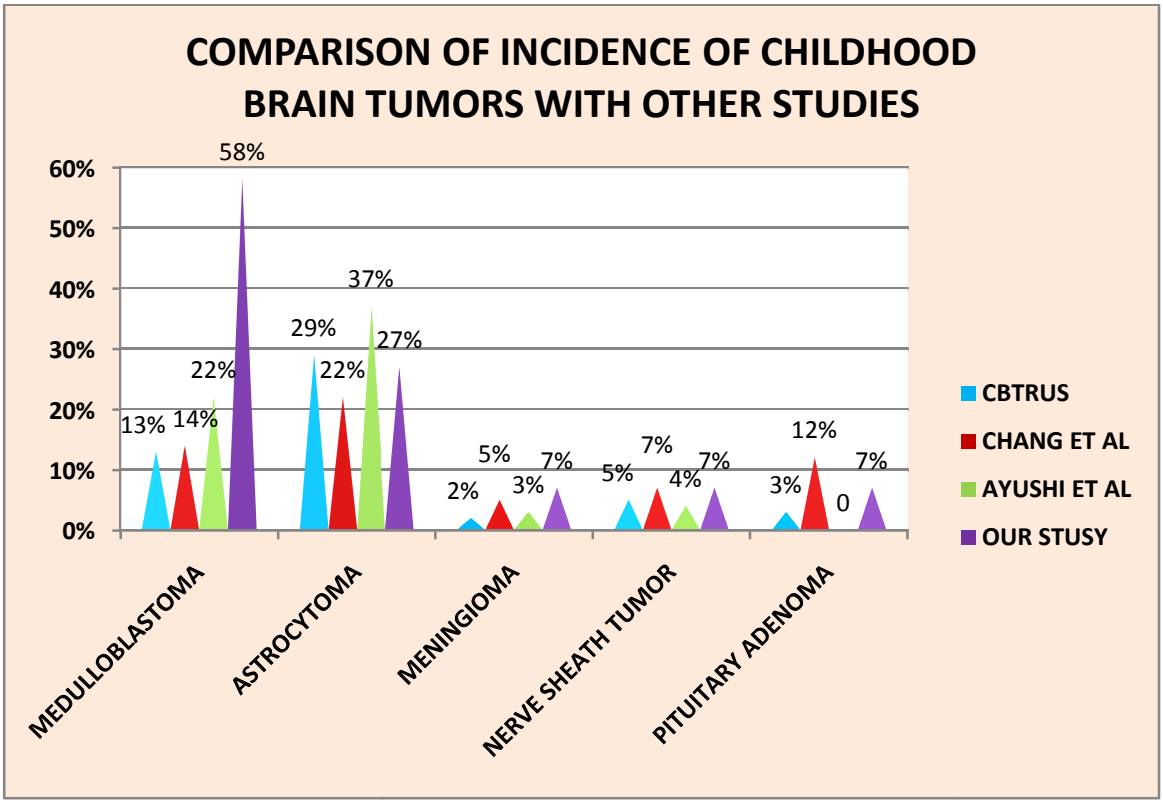
## Comparison of incidence of childhood brain tumors with other studies

| Tumor | CBTRUS | Chang et al | Mehedi et al | Ayushi et al | Manoharan et al | Our study |
|---|---|---|---|---|---|---|
| Medulloblastoma | 13% | 13.5% | 34.5% | 22.4% | 26.35 | 53.8% |
| Astrocytoma | 29.1% | 22% | 29% | 34.7% | 34.6% | 23.07% |
| meningioma | 1.9% | 5.3% | 2.2% | 3.2% | - | 7.69% |
| Nerve sheath tumor | 4.7% | 6.6% | - | 3.6% | 0% | 7.69% |
| Pituitary tumor | 3% | 11.5% | - | - | - | 7.69% |

The spectrum of childhood brain tumors in the present study (chart 16) showed a predominance of medulloblastoma which seem to contrast with all theinternational studies ( CBTRUS[14], Chang et al[16] (korea),Mehidi et al [68] (Morocco), Ayushi et al[4]) including the Indian study of Manoharan et al[75] who showed a predominance of Astrocytomas. The overall male to female ratio in all the studies of Cho KT et al[17], Farinotti et al[32], Mehrazin et al[69], Rickert CH et al[94], Wong TT et al[123] indicated that pediatric brain tumors are more common in males than in the females, which is in contrast with our study where females predominated (61.5%).

Over 90 % of the medulloblastoma typically arise from the superior medullary velum, grows and fills the cavity of the fourth ventricle. Dissemination to leptomeninges occurs in 10 -30 % and spread to the neuraxis occurs in < 10 %. Medulloblastoma is the most common malignant brain tumor in children. About 400 children are diagnosed with this tumor each year in the United States.The peak age of onset is between 5 -9 years of age.

## CHART – 16


COMPARISON OF INCIDENCE OF CHILDHOOD BRAIN TUMORS WITH OTHER STUDIES
60%
50%
40%
30%
20%
10%
0%
13%
14%
22%
58%
29%
22%
37%
27%
2%
5%
3%
7%
5%
7%
4%
7%
3%
12%
0
7%
MEDULLOBLASTOMA
ASTROCYTOMA
MENINGIOMA
NERVE SHEATH TUMOR
PITUITARY ADENOMA
CBTRUS
CHANG ET AL
AYUSHI ET AL
OUR STUSY

Most common malignant childhood tumor according to the studies of Mehdi et al[68] and Rosalva et al[99] is medulloblastoma (28.9%) with the peak incidence in the 5 -9 years age group. Out of the 13 cases of pediatric brain tumors in our study there were 7 cases of meduloblastomas. The mean age of occurrence of the tumor was in the 10 years.

Pediatric gliomas accounted for 52.6% of all brain tumors in children in the studies of Chang et al[16]. High grade gliomas including grade III and grade IV constitute about 14% in the study of Sri Gururangan et al[109], whereas GBM contributes to only 3% in the study of Chang and CBTRUS. In our study GBM accounts for 23.3 % of all childhood brain tumors. We reported 3 cases of high grade gliomas in our study out of which 2 cases of gliosarcoma was reported .

Gliosarcoma is a rare primary malignancy of CNS classified by the WHO as a high grade glioma and a variant of GBM with similar clinical presentation. According to Gilanis et al[34] gliosarcomas constitute to about 2% of glioblastomas. In contrast to other CNS tumors it can metastasise outside the neuraxis (Koul et al). Neoplastic cells of a glioblastoma divergently differentiate into spindle shaped collagen producing mesenchymal cells that form fascicles of sarcoma like tissue interspersed with pockets of more glial tumor cells creating a more distinct biphasic appearance.(BIOPSY INT). According to REIS et al[92] genetically gliosarcomas are similar to primary GBM except that they have not been shown to have amplification of EGFR the

sarcomatous element was originally thought to be a second malignant neoplasm arising from the perivascular fibroblasts in proliferating vessels, but it has been shown to have the same TP 53 and PTEN point mutation as the glial component suggesting a common origin. According to Kleihaues et al[53] gliosarcoma can occur at any age. It is uncommon in children and it peaks in 50-70 years age group.P Koul et al [79]also suggests the incidence to be in the same age group.

Gliosarcoma is a very rare tumor entity in children, but Michael Kareman[70] has reviewed 23 cases of pediatric gliosarcoma ( 4 cases from German HIT-GBM database and 19 cases from English medical science literature) and has concluded that it is more common in infants and in patients with history of previous cranial radiotherapy. He also observed that the median age of gliosarcoma to be 11 years. Kleihaues[53] stated that gliosarcoma occurring in the first and second decades show a predilection for males but female predominance is noted as age advances. Both cases in our study occurred in 15 years age group and both the cases were females.

Most common age of occurrence is the fourth – sixth decade.Age and sex incidence of gliosarcoma shows a peak in the first and second decade in the females following which the males show a predominance In our study two cases(2%) of gliosarcoma were reported which was in accordance with the study P.Koul et al[79] who showed an incidence of <2% of all gliomas. Both cases occurred in 15 years age group and both cases were females. Pediatric

gliosarcoma has been described with no difference in morphology or clinical features. It is more common in infants with previous history of radiotherapy. In his study Michael Karreman et al[70] showed a median age of occurence of gliosarcoma to be 11 years. As per the literature the gliosarcomas showed a strong predilection for the cerebral hemispheres in our study also.

In gliosarcoma the sarcomatous element resembled fibrosarcoma: the tumor cells were elongated and spindly and they organised into fascicles of parallel cells. Reticulin stains demonstrated a single cell pattern of reticulin positivity, whereas the pure glial areas of the same tumor was reticulin negative but stained positively for GFAP.[24] (fig 7,8)

Malignant meningiomas are uncommon comprising between 1 -2.8 % of meningiomas ( Mahmood et al[63], Jass et al[45]). Rhabdoid variant is an apparently recent addition to meningioma family. Keppes et al[125] in their studies have quoted that Rhabdoid meningioma was first described in 1998 as an unusual variant of meningioma and it is an histological indication of increased proliferation activity.

Histologically the descriptor rhabdoid refers to both the cytoplasm and nuclear configuration wherein gemistocyte appearing eosinophilic cytoplasm often shows displacement of nucleaus by spherical mass of intermediate filaments. This change may be present diffusely throughout the lesion or focal int he background of a more classical meningioma pattern. The pattern often

emerges during tumor progression and is therefore more obvious in recurrences than in the initial specimen.( Keppes et al)[125]. However Maier et al[64] have stressed that unless the rhabdoid cells constitute half or more of the lesion it does not meet he WHO 2007 criteria for the diagnosis of rhabdoid meningioma.

As per Douglas C Muller24 and Perry et al[81], pediatric meningiomas are distinctly rare but are more likely than adult counterpart to manifest aggressive behaviour or aggressive variant histologically and they lack any female predominance. Predisposing factors often include NF-2 or history of prior radiation, although half are still sporadic. In comparison with adult cases, clinical behaviour is more difficult to predict.

There were conflicting reports about the influence of age and gender on the proliferative potential and recurrences of meningiomas. Illiden et al[43] reported that age and gender has no influence on proliferative activity. Kosuya et al[50] reported that male gender was an important risk factor for high proliferative potential. As per Sasidhar et al[103] proliferative potential age and gender is not statistically significant. In the studies of E.Y.Kim et al[28] rhabdoid meningiomas occur mainly between 40-60 years with female predominance (75%). In contrast Mahmood et al[63] have stated that atypical and malignant meningiomas usually present earlier than benign meningiomas. Buccoleira et al[9] have one case of rhabdoid meningioma in a three years old child. In correlation with the above study we have encountered a case of pediatric rhabdoid

meningioma in a 10 years old child. But one special feature regarding the sex incidence is that in contrast to the lack of female predominance in aggressive pediatric meningiomas this case occurred in a female child.

There are some reports about the relationship of malignant meningiomas and higher incidence of cyst formation as per Guthrie BL[38]. Vassilouthis et al[118] have included cystic component as one of the CT criteria to evaluate histologic aggressiveness of meningiomas. But no such cystic component has been identified in our study.E.Y Kim et al[28] have commented the improved prognosis of rhabdoid meningiomas attributing to the added effect of adjuvant radiation therapy in their follow up period. Hence owing to its rarity each new case should be recorded to produce better clinical and pathological prognostic and therapeutic characterisation of these lesions.

Pituitary adenomas in children are relatively infrequent occurrences . most studies report the incidence of these tumors to be between 1 % and 10 % of all surgically treated adenomas. Despite the rarity of these tumors they can have a significant effect on the quality of life of the patient, especially during childhood, when the growth rates and development are at a peak. Christopher web et al[18] suggested the fact that most of the pituitary adenomas are secretory with prolactinomas being the most common type. They also reported that in there study 60 % were macroadenomas.

The clinical presentation of prolactinomas is sexually dimorphic with females presenting at a younger age with microadenomas, because they have a prolactin responsive breast and endometrial tissue, whereas the males present at a much older age group with macroadenomas with compressive symptoms like headache or visual problems . Kane LA et al[49] and Minderman Twilson et al[71] in their studies have evaluated that adenomas occurring in children are usually PRL or ACTH producing. In accordance , in our study we have reported one case of pituitary adenoma in a 10 years old child that presented as a macroadenoma (> 1cm) and was already evaluated outside as prolactinoma. Pediatric pituitary adenomas are quiet variable in their presentation.

Regarding the sex incidence as per Randall RV et al[89] and Christopher Web et al[18], most prolactinomas arise in women of reproductive age group. Reidl M et al[91] have stated that prolactinomas present at a older age in males. In contrast in our study we have encountered the incidence of prolactinoma in a pediatric male patient which goes along with the studies of Comb MC et al[67] who suggest that interestingly prolactinomas show no sex predilection. Lipper et al[57] has inferred that approximately in 10 % of cases presence of psammomatous calcification in hematoxylin and eosin stained section is a diagnostic clue and Webster et al has added that calcification in rare in other forms of adenoma. In our case of prolactinoma we did not observe this feature of calcification

## IMMUNOHISTOCHEMISTRY

Ki-67 is an intranuclear protein, which is present in the proliferating cells. It is present in the cells of all phases of cell cycle namely G1, S, G2 and M phase except G0 phase where the cells are in quiescent or resting stage. Thus, determination of Ki-67 is an excellent factor correlating cellular growth. MIB-1 labelling index is the number of Ki -67 labelled tumor nuclei expressed as a percentage of the total number of tumor nuclei counted. A total of atleast 1000 tumor nuclei were counted in in several areas where the positively stained nuclei were evenly distributed according to Torp SH et al[115] .

All Pathologist will quickly concede , counting mitotic figures in haematoxylin and eosin sections can be extremely cumbersome and time consuming, particularly if the specimen is large or tissue preservation is poor such that it is difficult to distinguish degenerating cells from mitosis Arrie Perry[85]

The WHO has resisted assigning any specific labelling index cutoffs in grading of individual tumor types because there is too much of interlaboratory variability . Wide ranging differences in staining results and counting methods making it difficult to extrapolate the results from one medical centre to another as per Johannesen et al[47], Prayson RA[86]. Arrie Perry and Danial Brat[85] in their text has stated that keeping in mind that each tumor type is different , a useful

though grossly oversimplified approach is to consider low, moderate and high proliferative indices as less than 5%, 5-10% and > 10% respectively

We evaluated the Ki 67 expression in various CNS tumors in our study. The expression of Ki-67 varied widely in each study and there is no specific cutoff levels to grade any CNS tumor. The variation in immunoreactivity may be due to different expression during the cell cycle. In our study the expression of Ki- 67 correlated well with the histological grade of all CNS tumors. The following table shows the labelling index in astrocytomas in our study in comparison to other studies.

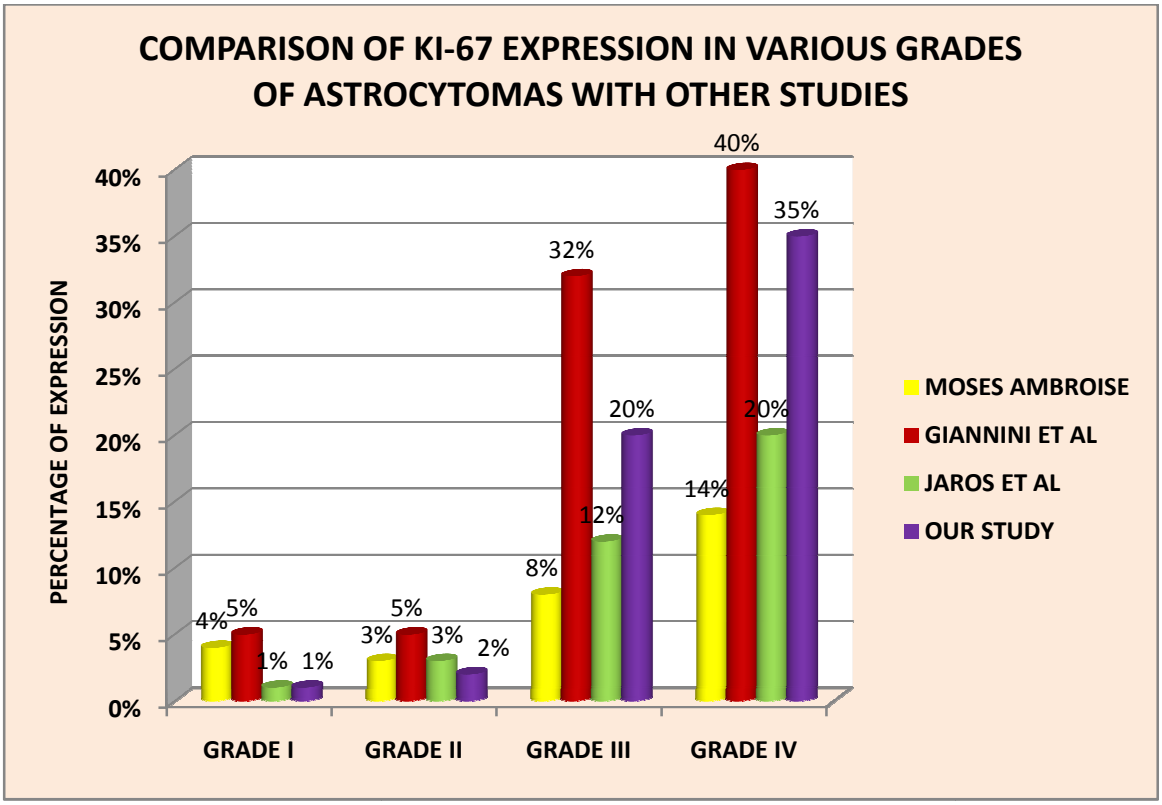
**Table – 21**

**Comparison of Ki-67 expression in various grades of of astrocytomas with other studies**

| STUDY | Grade I | Grade II | Grade III | Grade IV |
|---|---|---|---|---|
| Moses Ambroise et al[61] | 3.78 % | 2.76% | 7.45% | 13.85% |
| Wakimoto et al[119] | - | 3.8% | 18.4% | 31.6% |
| Rahti et al[90] | - | 1.75% | 8.74% | 20.54% |
| Ralte et al[88] | 0.44% | 3.73% | 9.65% | 10.33% |
| Tihan et al[114] | 1.83% | 3.7% | 11.4% | 20.2% |
| Rodriguez et al[97] | - | 10% | 34% | 46% |
| Giannini et al[36] | 4.8% | 5.2% | 32% | 40% |
| E Jaros et al[27] | 1 | 3 | 12 | 20 |
| **Our study** | **<1%** | **2%** | **20%** | **50%** |

In our study Ki- 67 expression did not exactly correlate with any of the other studies but It should be noted that the MIB -1 labelling index did correlate with the increasing tumor grade. All other studies[22, 41, 66] also showed a marked variation in there values. Ki-67 labelling index in our study can also be added

## CHART -17


COMPARISON OF KI-67 EXPRESSION IN VARIOUS GRADES OF ASTROCYTOMAS WITH OTHER STUDIES
PERCENTAGE OF EXPRESSION
40%
35%
30%
25%
20%
15%
10%
5%
0%
4%
5%
1%
1%
3%
5%
3%
2%
8%
32%
12%
20%
14%
40%
20%
35%
GRADE I
GRADE II
GRADE III
GRADE IV
MOSES AMBROISE
GIANNINI ET AL
JAROS ET AL
OUR STUDY

as a reference for future studies. Gliosarcoma ( grade IV astrocytoma) showed a maximum expression of Ki-67 (60 %) in our study indicating the high grade nature of the tumor with high proliferative activity.(chart -17)

Ki 67 expression in meningiomas also correlated well with their corresponding histological grades. The following table shows a comparison of Ki 67 labelling in meinigiomas with other studies.

**Table – 22**

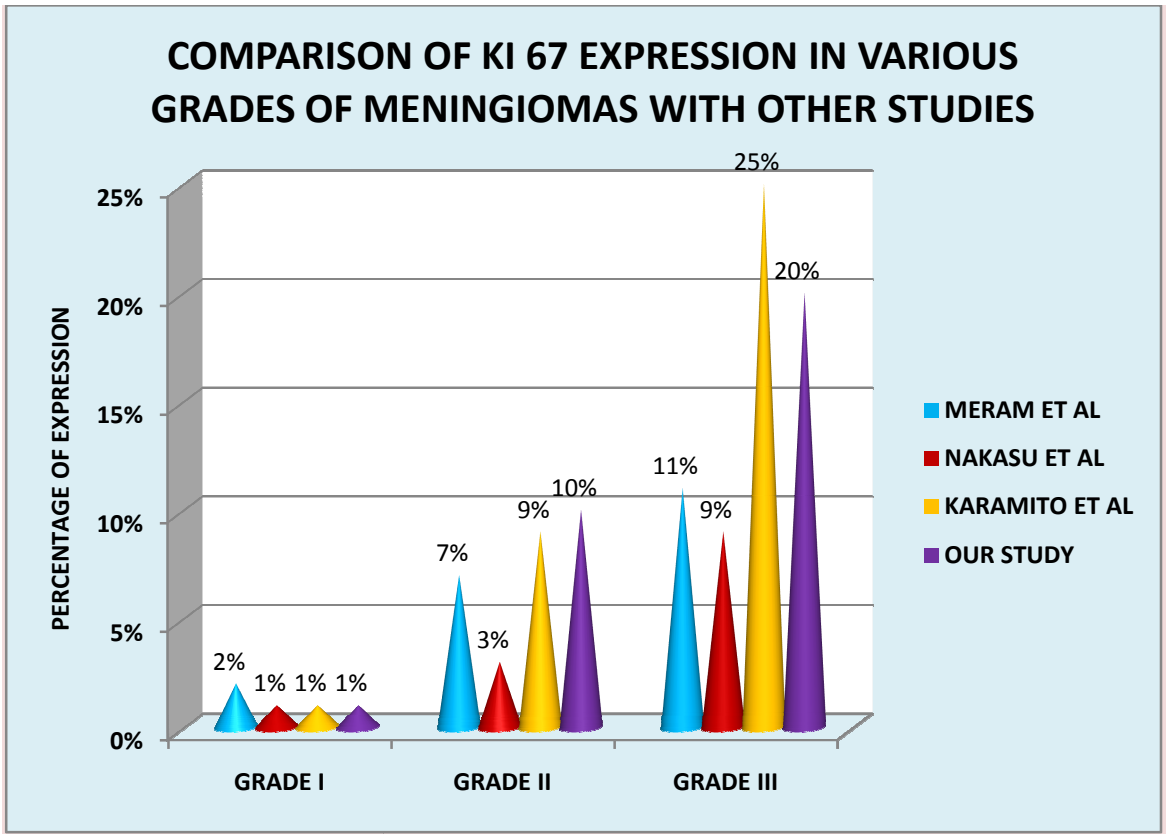
**Comparison of Ki-67 expression in different grades of meningiomas**

| Study | Grade I | Grade II | Grade III |
|---|---|---|---|
| Meram et al | 2.2% | 6.5% | 11.1% |
| Nakasu et al | 1% | 2.75% | 9% |
| Karamito poulou | 1.3% | 9.3% | 25% |
| Sashidhar babu et al[103] | 4% | 11.2% | 18.22% |
| **Our study** | **1%** | **10%** | **20%** |

According to the above table 22 and chart -18 it is seen that our study showed almost similar labelling index as in the studies of Sashidhar babu et al[103]. The labelling index correlated well with increasing grades of meningiomas as in the other stuies of Ohta M et al[78] and Pinnar Karbagli et al[83 87]. Kesavan et al[79] reported an expression of 20 % in a case of Rhabdoid meningioma ( Grade III) which was the same with or study too ( 20%)[100,106]

Oligodendroglioma being a grade II tumor showed a 0. 5 % expression of Ki 67 which correlated with the study of Jaros et al[27] who showed an

## CHART -18


COMPARISON OF KI 67 EXPRESSION IN VARIOUS GRADES OF MENINGIOMAS WITH OTHER STUDIES
PERCENTAGE OF EXPRESSION
25%
20%
15%
10%
5%
0%
2%
1%
1%
1%
7%
3%
9%
10%
11%
9%
25%
20%
GRADE I
GRADE II
GRADE III
MERAM ET AL
NAKASU ET AL
KARAMITO ET AL
OUR STUDY

expression of 0.6 % in oligodendrogliomas. This was also in accordance with the study of Coons SW et al[20,21] and the study of Kros JM et al [54]

In case of medulloblastoma the expression of Ki 67 was 5 % in our study. This percentage of expression of Ki 67 was less when compared with the study of Rosalva et al[99] who showed an average expression of 27.5%.

Ki 67 labelling was negative in case of ganglioglioma in our study. Wolf et al[122] in his study of 61 cases of gangliogliomas showed that in 74 % of cases the Ki 67 labelling index was < 1 %. He also showed that the labelling happened only in the astrocytic component of the tumor.

In case of pituitary adenoma the labelling was negative. According to Shrestha et al[80] and Prabin et al[84] Ki 67 expression in pituitary adenomas is often <1 %. But Luciano et al[60] in his study showed a slightly higher expression of Ki 67 in the range of 2.72 ± 2.49 %.

Ki 67 expression was less than 1 % in case of hemangioblastoma. This value correlated with the study of Miyagami M et al[72] who showed a mean expression of 0.8 % in hemangioblastomas.

According to the study of Huma Arshad[42] and Suri S Vaishali et al[111] the labelling index in case of ependymomas was 0.5 %. In our study the value was 1 %. Nerve sheath tumor usually showed a very low expression of Ki -67 and it was about 2% in the study of Saito et al[101]. In our study Ki 67 expression was < 0.1 %. Jaros et al[27] also showed a similar expression of 0.2 %.

The caveats of immunohistochemical analysis using Ki-67 include different antigens, background staining and inhomogeneous staining that can contribute to interlaboratory and interobservwer variations[3]. The archieved specimens may lose its antigenicity over time and cannot be retrieved adequately and thus giving a false low labelling index.

# *CONCLUSION*

# CONCLUSION

In this retrospective study of 100 Central Nervous system tumors that were evaluated with histochemical, histopathological and immunohistochemistry, the following were the conclusions made and presented.

1. The incidence of central nervous system tumors is
2. High incidence of CNS neoplasms is seen in the 3rd and 4th decade with slight male predominance.
3. Primary CNS tumors commonly occurs supratentorially in adults and infratentorially in children.
4. Astrocytomas constitute the most common CNS tumor, followed by meningiomas.
5. Grading of astrocytomas showed that grade IV tumors are more common.
6. In children Medulloblastomas are the commonest neoplasm.
7. Special stains help in the confirmation of certain neoplasms.
8. Ki-67 has a great value in the histological assessment of neoplastic lesions of the CNS. It has to be used prudently in combination with histopathological features for designating the exact grade of the tumor

In developing countries like India due to lack of complete registration of newly diagnosed cases of CNS tumors with local cancer registries the exact

tumor burden goes unnoticed and is underestimated. Hospital based prevalence data therefore forms the basis for estimating the tumor burden and is essential for ascertaining the required health care infrastructure in the management of these cancers. This can have important connotations in the field of brain tumor research particularly when analysing the geographical differences in their molecular and genetic profiles which could aid in the development of targeted individualised therapies and planning treatment protocols and strategies.

# *ANNEXURES*

# ANNEXURE-I

# WHO CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS

## TUMORS OF THE NEUROEPITHELIAL TISSUE

### ASTROCYTIC TUMORS

| | | | |
|---|---|---|---|
| 1. | 9421/1 | Pilocytic astrocytoma | WHO grade I |
| | 9425/3 | Pilomyxoid astrocytoma | WHO grade II |
| 2. | 9384/1 | Subependymal Giant Cell Astrocytoma | WHO grade I |
| 3. | 9424/3 | Pleomorphic Xanthoastrocytoma | WHO grade II |
| 4. | 9400/3 | Diffuse Astrocytoma | WHO grade II |
| | 9420/3 | Fibrillary Astrocytoma | |
| | 9411/3 | Gemistocytic Astrocytoma | |
| | 9410/3 | Protoplasmic Astrocytoma | |
| 5. | 9401/3 | Anaplastic Astrocytoma | WHO grade III |
| 6. | 9440/3 | Glioblastoma | WHO grade IV |
| | 9441/3 | Giant cell Glioblastoma | WHO grade IV |
| | 9442/3 | Gliosarcoma | WHO grade IV |
| 7. | 9381/3 | Gliomatosis Cerebri | |

### OLIGODENDROGLIAL TUMORS

| | | | |
|---|---|---|---|
| 8. | 9450/3 | Oligodenroglioma | WHO grade II |
| 9. | 9451/3 | Anaplastic Oligodenroglioma | WHO grade III |

### OLIGOASTROCYTIC TUMORS

| | | | |
|---|---|---|---|
| 10. | 9382/3 | Oligoastrocytoma | WHO grade II |
| 11. | 9382/3 | Anaplastic Oligoastrocytoma | WHO grade III |

### EPENDYMAL TUMORS

| | | | |
|---|---|---|---|
| 12. | 9383/1 | Subependymoma | WHO grade I |
| 13. | 9394/1 | Myxopapillary Ependymoma | WHO grade I |
| 14. | 9391/3 | Ependymoma | WHO grade II |
| | 9391/3 | Cellular | |
| | 9393/3 | Papillary | |
| | 9391/3 | Clear cell | |
| | 9391/3 | Tanycytic | |
| 15. | 9392/3 | Anaplastic Ependymoma | WHO grade III |

### CHOROID PLEXUS TUMORS

| | | | |
|---|---|---|---|
| 16. | 9390/0 | Choroid plexus papilloma | WHO grade I |
| 17. | 9390/1 | Atypical choroid plexus papilloma | WHO grade II |

18.9390/3 Choroid plexus carcinoma WHO grade III

**OTHER NEUROEPITHELIAL TUMORS**

19.9430/3 Astroblastoma WHO grade I
20.9444/1 Chordoid glioma of the third ventricle WHO grade II
21.9431/1 Angiocentric glioma WHO grade I

**NEURONAL AND MIXED NEURONAL- GLIAL TUMORS**

22.9493/0 Dysplastic Gangliocytoma of cerebellum (Lhermitte- Duclos)
23.9412/1 Desmoplastic infantile astrocytoma/Ganglioglioma WHO gr I
24.9413/0 Dysembryoplastic neuroepithelial tumor WHO grade I
25.9492/0 Gangliocytoma WHO grade I
26.9505/1 Ganglioglioma WHO grade I
27.9505/3 Anaplastic Ganglioglioma WHO grade III
28.9506/1 Central neurocytoma WHO grade II
29.9506/1 Extraventricular neurocytoma WHO grade II
30.9506/1 Cerebellar liponeurocytoma WHO grade II
31.9509/1 Papillary Glioneuronal tumor WHO grade I
32.9509/1 Rosette forming Glioneuronal tumor of the fourth ventricle gr I
33.8680/1 Paraganglioma WHO grade I

**TUMORS OF THE PINEAL REGION**

34.9361/1 Pineocytoma WHO grade I
35.9362/3 Pineal parenchymal T of the intermediate differentiation
WHO grade II,III
36.9362/3 Pineoblastoma WHO grade IV
37.9395/3 Papillary tumor of the pineal region WHO grade II,III

**EMBRYONAL TUMORS**

38.9470/3 Medulloblastoma WHO grade IV
9471/3 Desmoplastic/Nodular medulloblastoma
9471/3 Medulloblastoma with extensive nodularity
9474/3 Anaplastic Medulloblastoma
9474/3 Large cell Medulloblastoma
39.9473/3 CNS Primitive neuroectodermal tumor WHO grade IV
9500/3 CNS Neuroblastoma
9490/3 CNS Ganglioneuroblastoma
9501/3 Medulloepithelioma
9392/3 Ependymoblastoma
40.9508/3 Atypical teratoid /Rhabdoid tumor WHO grade IV

**TUMORS OF THE CRANIAL AND SPINAL NERVES**

41.9560/0 Schwannoma WHO grade I
9560/0 Cellular

| | | | |
|---|---|---|---|
| | 9560/0 | Plexiform | |
| | 9560/0 | Melanotic | |
| 42. | 9540/0 | Neurofibroma | WHO grade I |
| | 9550/0 | Plexiform | |
| 43. | 9571/0 | Perineurioma NOS | WHO grade I,II,III |
| | 9571/3 | Malignant Perineurioma | |
| 44. | Malignant peripheral nerve sheath tumor (MPNST) | | WHO grade II, III, IV |
| | 9540/3 | Epithelioid MPNST | |
| | 9540/3 | MPNST with mesenchymal differentiation | |
| | 9540/3 | Melanotic MPNST | |
| | 9540/3 | MPNST with glandular differentiation | |

**TUMORS OF THE MENINGES**

**Tumors of the meningothelial cells**

| | | | |
|---|---|---|---|
| 45. | 9530/0 | Meningioma | WHO grade I |
| | 9531/0 | Meningothelial | |
| | 9532/0 | Fibrous (fibroblastic ) | |
| | 9537/0 | Transitional (mixed) | |
| | 9533/0 | Psammomatous | |
| | 9534/0 | Angiomatous | |
| | 9530/0 | Microcystic | |
| | 9530/0 | Secretory | |
| | 9530/0 | Lymphoplasmacyte – rich | |
| | 9530/0 | Metaplastic | |
| | 9538/1 | Chordoid | WHO grade II |
| | 9538/1 | Clear cell | WHO grade II |
| | 9539/1 | Atypical | WHO grade II |
| | 9538/3 | Papillary | WHO grade III |
| | 9538/3 | Rhabdoid | WHO grade III |
| | 9530/3 | Anaplastic ( malignant) | WHO grade III |

**Mesenchymal tumors**

| | | |
|---|---|---|
| 46. | 8850/0 | Lipoma |
| 47. | 8861/0 | Angiolipoma |
| 48. | 8880/0 | Hibernoma |
| 49. | 8850/3 | Liposarcoma |
| 50. | 8815/0 | Solitary fibrous tumor |
| 51. | 8810/3 | Fibrosarcoma |
| 52. | 8890/0 | Malignant fibrous histiocytoma |
| 53. | 8890/0 | Leiomyoma |
| 54. | 8890/3 | Leiomyosarcoma |
| 55. | 8900/0 | Rhabdomyoma |
| 56. | 8900/3 | Rhabdomyosarcoma |
| 57. | 9220/0 | Chondroma |

58.9220/3 Chondrosarcoma
59.9180/0 Osteoma
60.9180/3 Osteosarcoma
61.9210/0 Osteochondroma
62.9120/0 Hemangioma
63.9133/1 Epithelioid Hemangioendothelioma
64.9150/1 Hemangiopericytoma WHO grade II
65.9150/1 Anaplastic hemangiopericytoma WHO grade III
66.9120/3 Angiosarcoma
67.9364/3 Kaposi Sarcoma
68.9364/3 Ewing Sarcoma – PNET

**PRIMARY MELANOCYTIC LESIONS**

69.8728/0 Diffuse melanocytosis
70.8728/1 Melanocytoma
71.8720/3 Malignant melanoma
72.8728/3 Meningeal melanomatosis

**OTHER NEOPLASMS RELATED TO THE MENINGES**

73.9161/1 Hemangioblastoma WHO grade I

**TUMORS OF THE HEMATOPOETIC SYSTEM**

74.9590/3 Malignant Lymphoma
75.9731/3 Plasmacytoma
76.9930/3 Granulocytic Sarcoma

**GERM CELL TUMORS**

77.9064/3 Germinoma
78.9070/3 Embryonal Carcinoma
79.9071/3 Yolk sac tumor
80.9100/3 Choriocarcinoma
81.9080/1 Teratoma
9080/0 mature
9080/3 immature
9084/3 Teratoma with malignant transformation
82.9085/3 mixed germ cell tumors

**TUMORS OF THE SELLAR REGION**

83.9350/1 Craniopharyngioma WHO grade I
9351/1 Adamantinomatous
9352/1 Papillary
84.9582/0 Granular cell tumor WHO grade I
85.9432/1 Pituicytoma WHO grade I
86.8991/0 Spindle cell oncocytoma of the adenohypophysis WHO grade I

# ANNEXURE-II

# MASTER CHART

| S.no | Patho no | Age/sex | Site | Clinical diagnosis | HPE diagnosis | WHO grade |
|---|---|---|---|---|---|---|
| 1 | 261/10 | 48/M | parietal | ? tuberculoma | GBM | IV |
| 2 | 263/10 | 35/F | Tentorium | meningioma | Meningothelial meningioma | I |
| 3 | 265/10 | 45/F | Parietal | meningioma | Transitional meningioma | II |
| 4 | 326/10 | 55/F | Temporal | SOL | Astrocytoma | II |
| 5 | 393/10 | 45/F | Parietal | meningioma | Transitional meningioma | I |
| 6 | 433/10 | 19/M | Occipital | SOL | Astrocytoma | III |
| 7 | 478/10 | 16/M | Posterior fossa | SOL | medulloblastoma | IV |
| 8 | 479/10 | 19/M | D9-D10 | SOL | Schwannoma | I |
| 9 | 555/10 | 52/M | Frontal | glioma | Astrocytoma | III |
| 10 | 577/10 | 30/F | Frontal | SOL | Anaplastic meningioma | III |
| 11 | 668/10 | 54/F | Frontal | meningioma | Meningothelial meningioma | I |
| 12 | 881/10 | 52/M | Frontal | Glioma | Astrocytoma | IV |
| 13 | 882/10 | 40/F | Parietal | SOL | Adenocarcinoma deposit | - |
| 14 | 915/10 | 45/M | Thalamus | glioma | Astrocytoma | IV |
| 15 | 1149/10 | 45/M | Frontal | ? GBM | GBM | IV |
| 16 | 1374/10 | 48/F | CP Angle | ? Schwannoma | Schwannoma | I |
| 17 | 1399/10 | 40/F | Parietal | SOL | Astrocytoma | III |
| 18 | 1437/10 | 35/F | Temporal | SOL | Astrocytoma | I |
| 19 | 1439/10 | 55/F | sphenoid | meningioma | Meningothelial meningioma | I |
| 20 | 1621/10 | 50/M | Skull base tumor | SOL | Astrocytoma | II |
| 21 | 1660/10 | 40/F | Frontal | ? GBM | Astrocytoma | II |
| 22 | 1831/10 | 58/M | Parietal | Astrocytoma | Astrocytoma | III |
| 23 | 1952/10 | 32/M | Frontal | SOL | Ependymoma | II |
| 24 | 1967/10 | 35/F | Tentorial | meningioma | Anaplastic meningioma | III |

| | | | | | | |
|---|---|---|---|---|---|---|
| 25 | 2141/10 | 45/F | Frontal | GBM | Astrocytoma | IV |
| 26 | 2236/10 | 72/M | Temporal | SOL | Astrocytoma | IV |
| 27 | 2307/10 | 33/M | Parietal | SOL | Astrocytoma | IV |
| 28 | 2401/10 | 51/M | Frontal | SOL | Astrocytoma | II |
| 29 | 2452/10 | 32/F | Sellar fossa | SOL | Pituitary adenoma | I |
| 30 | 2487/10 | 7/M | Posterior fossa | medulloblastoma | Medulloblastoma | IV |
| 31 | 2526/10 | 14/M | Posterior fossa | SOL | Medulloblastoma | IV |
| 32 | 2636/10 | 70/M | Suprasellar | SOL | Pituitary adenoma | I |
| 33 | 2738/10 | 11/M | Posterior fossa | SOL | Medulloblastoma | IV |
| 34 | 2814/10 | 45/M | Temporal | SOL | Astrocytoma | I |
| 35 | 3353/10 | 29/F | Parietal | meningioma | Meningothelial meningioma | I |
| 36 | 3482/10 | 10/F | Posterior fossa | medulloblastoma | Meduloblastoma | IV |
| 37 | 3683/10 | 50/F | Parietal | SOL | Astrocytoma | IV |
| 38 | 3686/10 | 53/M | Frontal | ?GBM | Astrocytoma | IV |
| 39 | 3739/10 | 6/F | Posterior fossa | medulloblastoma | Medulloblastoma | IV |
| 40 | 3741/10 | 68/F | D8-D9 | ? meningioma | Psammomatous meningioma | I |
| 41 | 3816/10 | 45/M | Occipital | ? secondaries | Adenocarcinomatous deposit | - |
| 42 | 3822/10 | 40/F | Sphenoid wing | ? meningioma | Transitional meningioma | I |
| 43 | 3859/10 | 38/F | CP angle | ? schwannoma | Schwannoma | I |
| 44 | 3990/10 | 40/M | Parietal | ? astrocytoma | GBM | IV |
| 45 | 4128/10 | 62/M | Temporal | SOL | Astrocytoma | III |
| 46 | 4211/10 | 42/M | CP angle | Schwannoma | Schwannoma | I |
| 47 | 4258/10 | 37/F | Suprasellar | Meningioma | Meningothelial meningioma | I |
| 48 | 7/11 | 55/M | D12-L1 | Ependymoma | Myxopapillary ependymoma | I |
| 49 | 100/11 | 65/M | L2-L3 | ? neurofibroma | Schwannoma | I |
| 50 | 233/11 | 38/M | Parietal | SOL | Astrocytoma | II |
| 51 | 272/11 | 33/M | Parietal | glioma | Astrocytoma | II |
| 52 | 504/11 | 56/F | Temporal | Astrocytoma | Astrocytoma | III |
| 53 | 723/11 | 9/F | D1-D3 | SOL | Neurofibroma | I |
| 54 | 734/11 | 40/F | Occipital | GBM | Astrocytoma | IV |
| 55 | 830/11 | 10/M | Supra sellar | SOL | Pituitary adenoma | I |
| 56 | 834/11 | 65/M | Sphenoid wing | Meningioma | Transitional meningioma | I |
| 57 | 1110/11 | 12/M | Posterior fossa | medulloblastoma | Medulloblastoma | IV |
| 58 | 1167/11 | 35/F | Sellar | SOL | Pituitary adenoma | I |
| 59 | 1383/11 | 13/F | Frontal | SOL | GBM | IV |
| 60 | 1416/11 | 65/M | Parietal | SOL | Hemangioblastoma | I |
| 61 | 1561/11 | 33/M | Frontal | SOL | Atypical meningioma | III |
| 62 | 1839/11 | 45/F | Parietal | SOL | Psammomatous meningioma | I |
| 63 | 1951/11 | 26/M | Parietal | SOL | Astrocytoma | III |
| 64 | 2030/11 | 30/M | Temporal | Glioma | Astrocytoma | III |

| | | | | | | |
|---|---|---|---|---|---|---|
| 65 | 2031/11 | 23/M | Posterior fossa | Recurrent SOL | Hemangioblastoma | I |
| 66 | 2032/11 | 26/M | C5-C6 | Neurofibroma | Neurofibroma | I |
| 67 | 2484/11 | 40/M | Parietal | Glioma | Astrocytoma | I |
| 68 | 2630/11 | 26/M | Frontal | Glioma | Astrocytoma | III |
| 69 | 2771/11 | 55/F | Parietal | ? meningioma | Transitional meningioma | I |
| 70 | 2890/11 | 55/F | L1-L2 | neurofibroma | neurofibroma | I |
| 71 | 2936/11 | 53/F | Frontal | meningioma | Meningothelial meningioma | I |
| 72 | 3055/11 | 35/F | D1-D3 | SOL | MPNST- low grade | II |
| 73 | 3303/11 | 30/M | CP angle | SOL | Schwannoma | I |
| 74 | 3380/11 | 45/M | Frontal | SOL | Meningothelial meningioma | I |
| 75 | 3401/11 | 35/F | Parietal | SOL | Meningothelial meningioma | I |
| 76 | 3523/11 | 26/F | Parietal | Glioma | Astrocytoma | III |
| 77 | 3730/11 | 43/M | Frontal | GBM | Astrocytoma | IV |
| 78 | 3841/11 | 28/F | Frontal | Glioma | Astrocytoma | IV |
| 79 | 3929/11 | 42/M | Frontal | Glioma | Ganglioglioma | I |
| 80 | 4113/11 | 48/F | Frontal | ? meningioma | Meningioma | I |
| 81 | 4327/22 | 29/M | Parietal | Gliotic cyst | Astrocytoma | IV |
| 82 | 4535/11 | 15/F | Frontal | ? meningioma | Gliosarcoma | IV |
| 83 | 4670/11 | 55/F | Frontal | ? meningioma | Transitional meningioma | I |
| 84 | 215/12 | 25/F | Frontal | Glioma | Astrocytoma | IV |
| 85 | 217/12 | 30/M | Parietal | Glioma | Oligodendroglioma | I |
| 86 | 295/12 | 30/M | Parietal | Glioma | Astrocytoma | II |
| 87 | 299/12 | 80/F | Parietal | Meningioma | Transitional meningioma | I |
| 88 | 338/12 | 15/F | Frontal | GBM | Gliosarcoma | IV |
| 89 | 390/12 | 20/M | D7-D8 | SOL | Schwannoma | I |
| 90 | 500/12 | 49/M | CP angle | SOL | Schwannoma | I |
| 91 | 539/12 | 35/M | Temporal | SOL | Astrocytoma | II |
| 92 | 628/12 | 23/F | temporal | SOL | Astrocytoma | II |
| 93 | 819/12 | 55/F | Temporal | ? meningioma | Astrocytoma | IV |
| 94 | 909/12 | 65/F | Parietal | Meningioma | Meningothelial meningioma | I |
| 95 | 934/12 | 47/M | Frontal | SOL | Astrocytoma | III |
| 96 | 1261/12 | 10/F | Temporal | SOL | Rhabdoid meningioma | III |
| 97 | 1380/12 | 40/M | Frontal | SOL | Astrocytoma | III |
| 98 | 1475/12 | 27/F | Frontal | ? glioma | Astrocytoma | III |
| 99 | 1537/12 | 40/M | CP Angle | SOL | schwannoma | I |
| 100 | 1827/12 | 47/M | Parietal | SOL | Astrocytoma | IV |

## ANNEXURE-III

## HAEMATOXYLIN AND EOSIN

**Preparation of the solution – HARRIS HEMATOXYLIN**

- Distilled water - 1000 ml
- Ammonium alum - 100 g
- Haematoxylin - 5 g
- Absolute ethyl alcohol – 50 ml
- Mercuric oxide – 2.5 g

100 g of ammonium alum dissolved in 1000 ml of distilled water by heating and shaking at 60 $^{0}$C. Add solution of 50 g of haematoxylin in 50 ml of ethyl alcohol and bring rapidly to boil. When it begins to boil, remove from flame and add 2.5 g of mercuric oxide. Mix by swirling gently.

**EOSIN STAIN:**

- Eosin Y – 1 g
- Distilled water – 20 ml
- 95% ethanol -80 ml
- Glacial acetic acid -0.2 ml

Dissolve 1 g eosin Yin 20 ml of water and add 95% ethanol and glacial acetic acid

**PROCEDURE:**

1. Bring sections to water
2. Stain with Harris hematoxylin for 15 minutes.
3. Rinse in tap water
4. Differentiate with 1% acid alcohol – 3 to 10 quick dips
5. Rinse in tap water briefly
6. Allow for blueing in tap water.
7. Stain with 1% aqueous eosin Y for 15 seconds
8. Wash in tap water
9. Dehydrate in ascending grades of alcohol
10. Clear with xylene
11. Mount with DPX

## ANNEXURE- IV

## RETICULIN STAINING

**Preparation of solution:**

- 1% potassium permanganate
- 2%  Potassium metabisulphite
- 2% Ferric Ammonium Sulphate
- 10% Formalin neutral
- 0.2% Gold chloride
- 2.55 sodium thiosulphate
- 10% KOH
- Ammoniacal silver solution.

Preparation of ammoniacal silver solution:

- 10%  AgNO3 - 40 ml
- 10%  KOH  - 10 ml
- Add 40 ml of 10 % Ag NO3 to 10 ml of 10 % KOH in a flask, allow silver to deposit
- Remove the supernatant fluid
- Wash the deposit with distilled water several times
- Add strong ammonia drop by drop until the solution takes a faint sheen
- Make the solution to twice its volume by the distilled water

**Procedure:**

- Section to water
- Oxidize in potassium permanganate – 2 minutes
- Rinse in water
- Decolourize in potassium meta bisulphate – 1 minute
- Prolonged wash in water – 5 minutes.
- Sensitise in ferric ammonium sulphate – 1 minute.
- Prolonged wash in tap water followed by 2 changes of distilled water.
- Impregate in ammoniiacal silver solution – 1 minute.

## ANNEXURE- V
## IMMUNOHISTOCHEMISTRY

Preparation of Tris Buffered Saline ( TBS): 0.005 M TBS
Distilled water – 10 litres
Sodium chloride -80 g
TRIS (H ydroxymethylamine) – 6.05 g
1 M Hcl – 44 ml
Final pH is adjusted to 7.6 with either 1 M Hcl or 0.2 M tris solution
Preparation of CITRATE buffer solution ( Antigen retrieval solution):
Trisosium citrate – 2.94 g
1 N Hcl – 5 ml
Distilled water- 1000 ml
Final pH is adjusted to 6.0 with 1N Hcl
Antigen retrieval:
The slides are placed in citrate buffer in the coplin jar and capped. The jar is then heated in a 750 W domestic microwave oven for 15 minutes. 5 minutes in low power(40), 5 minutes in medium power (60) and 5 minutes in full power (80) pausing only to top up the fluid

**Procedure:**

1. Dewax the section in xylene( ½ hr , two changes) and bring sections to distilled water.
2. Antigen retrieval using TBS by microwave oven heating
3. Cool to room temperature in running tap water for 20 minutes
4. Bring sections to TBS for 5 minutes
5. Drain and wipe off excess TBS around sections
6. Incubate in endogenous peroxidise blocking reagents for 15-20 minutes
7. Gently wash the slides in TBS for 5 minutes
8. Wipe off the excess fluid and incubate with power block for 15 -20 minutes.
9. Wipe off the excess fluid and incubate with primary antibody for 60 minutes.
10. Repeat steps 4 and 5.
11. Incubate with super enhancer for 30 minutes
12. Repeat steps 4 and 5.

13. Incubate with secondary antibody
14. Repeat steps 4 and 5.
15. Incubate in DAB ( Diaminobenzidine) substrate solution for 2-10 minutes. ( To prepare DAB add 1 ml of substrate buffer, 1 drop of liquid DAB)
16. Wash in distilled water, counterstain with Haematoxylin, clear in xylene and mount with DPX.

**RESULTS:**

Tumor marker- Brown

Nucleus - blue

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